DUPLICATE

Vol. 27 No. 136 December, 1952

ARCHIVES OF DISEASE IN CHILDHOOD

INCORPORATING THE BRITISH JOURNAL OF CHILDREN'S DISEASES

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LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

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TWO CASES OF CYTOMEGALIC INCLUSION ENCEPHALITIS

BY

A. M. G. CAMPBELL, JOAN GUY and W. GREY WALTER

From the Department of Child Health, Bristol University

(RECEIVED FOR PUBLICATION JUNE 27, 1952)

In 1934 Dawson described a new type of encephalitis with a distinctive clinical and pathological picture which has been recognized periodically during the last few years and has been well reviewed by Greenfield (1950) and other authors.

This disease is usually found in children and in most cases pursues an unrelenting course of weeks or months to death. It is impossible to conjecture as to whether any patients ever recover.

The disease always begins with mental symptoms and in the majority of cases there are severe myoclonic spasms. A feature of the disease is the normal cerebrospinal fluid apart from the high incidence of a paretic Lange reaction. The pathological picture is characteristic and in many cases acidophilic inclusion bodies have been found in the nerve cells of the brain.

We propose to describe two cases in children, not because they show many new factors but because we feel that paediatricians may still be unaware of the disease, which is probably somewhat commoner than is imagined, and because a summary of its clinical and pathological features brings out a fairly constant clinical picture which makes diagnosis during life a possibility.

Case Reports

Case 1.—B.W., aged 11 years, was admitted to hospital on May 9, 1951. She was the elder of two children, her brother, aged 7, being asthmatic. Both parents are alive and well, though her mother suffers from rheumatoid arthritis.

In July, 1950, she had a severe insect bite on the leg, which became septic and necessitated out-patient treatment.

From August, 1950, onwards her parents noticed a change in her temperament and in her facial expression. She became listless and apathetic, and, always backward at school, her progress deteriorated. In December, 1950, she had a vague febrile illness lasting three weeks, characterized by headache, aching limbs and nasal catarrh. Afterwards she continued to complain of occasional headaches.

On March 16, 1951, she was knocked down by a bicycle. She sustained a cut on the forehead and was dazed, but did not lose consciousness. Though she vomited once after the accident she appeared to recover completely. Two weeks later her mother noticed that she seemed to be in a 'dreamy state'. Later that day she fell down several times for no apparent reason. There was nothing to suggest that she had either fainted or had a fit.

From that time onwards she continued to stumble and fall. Her movements became clumsy and jerky and she had difficulty in dressing herself. Personality changes persisted; she developed a facile smile, became reluctant to talk and answered questions slowly. When sent on an errand, she returned having purchased nothing and holding a 10s. note in the air. Her headaches became more frequent and she had a tendency to vomit.

On examination she was seen to be a tall, thin girl with a vague, dreamy expression. Reluctant to speak spontaneously, she was cooperative and answered questions sensibly, though her speech was slightly jerky. She made occasional fidgety movements. There was some facial asymmetry, the right side of the face moving less than the left.

Her gait was unsteady and she showed some muscular hypotonicity and incoordination. Romberg's sign was negative. The right knee jerk was brisker than the left. The ankle jerks were not obtained. The plantar responses were flexor. Sensation was difficult to assess as the patient answered slowly and did not always appear to understand. The pupils, which were crescentic, reacted to light. The ocular fundi were normal apart from a suggestion of pallor of the left disc. Examination of other systems showed no abnormality.

An investigation for toxoplasmosis was negative.

The Mantoux test (1 : 100) was negative, as also were the Wassermann and Kahn reactions.

Radiographs of the skull, sinuses and chest were normal.

The erythrocyte sedimentation rate was 7 mm. in one

hour. A blood count gave Hb., 100%; leucocytes, 4,300 (polymorphs 75%, lymphocytes 24%, monocytes 1%).

Examination of the cerebrospinal fluid showed a pressure of 300 mm., and a clear, colourless fluid with one white cell per c.mm., and 15 mg. protein per 100 ml. Globulin was not increased. The Lange curve was normal.

ELECTRO-ENCEPHALOGRAPHY.—Records were taken on April 17 and 19, 1951. A six-channel apparatus was used with an automatic wave analyser. The electrode placements and instrument settings were as indicated in Fig. 1A and B. The results were the same on both occasions.

deep in to the head from the temporal region on both sides, was responsible for the sharp wave; the other, antero-posteriorly oriented, gave rise to the slow wave, which had a duration of 1·25 seconds.

Electromyograms showed that the muscle groups involved in the jerking were mainly the extensors of the left arm and right leg but all groups participated from time to time. The cerebral discharges were so constant in their wave-forms that when superimposed there was complete identity even to minute details in their pattern (Fig. 2A and B).

The repetition rate of the cerebral discharge was also unusually regular, varying from six to 20 seconds.

Such unvarying regularity is perhaps the most com-

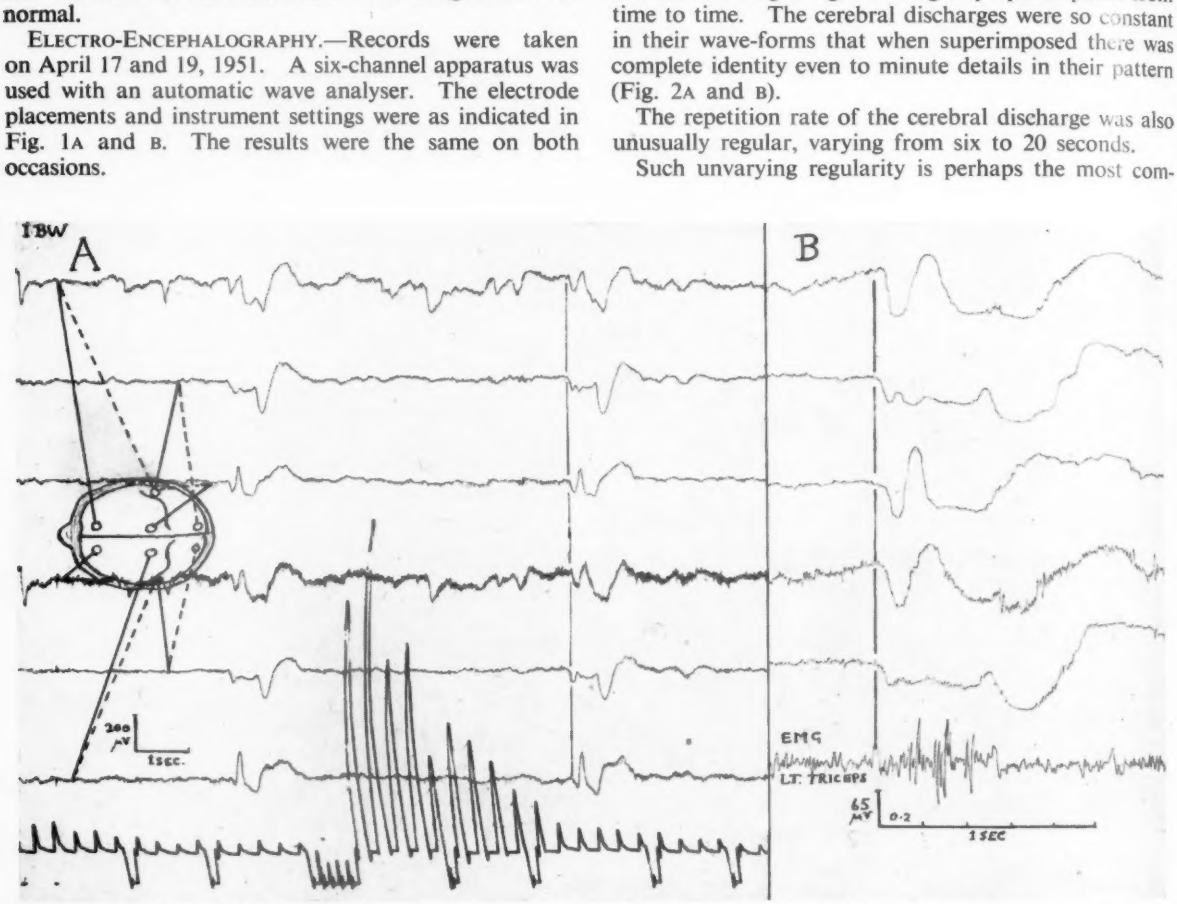

FIG. 1.—A. E.E.G. taken at low speed and reduced amplification showing two of the complexes. The differing wave-forms in the various channels indicate a complex generator and the symmetry of the two hemispheres a subcortical origin. B. At higher speed and amplification the wave-form is displayed more clearly and the time relation to the muscular spasm can be observed.

In the occipital regions there were moderate-sized alpha rhythms at 7-8 c/s. attenuated by visual activity and somewhat larger on the right side; far more prominent than these normal rhythms were very large (200 microvolt) intermittent sharp-and-long wave discharges which appeared at intervals of six to 20 seconds, and were accompanied by myoclonic spasms of the limbs (Fig. 1).

The discharges were most evident in the temporal regions of both hemispheres and special studies were made to work out the geometry of the equivalent generators responsible for these cerebral discharges, and the peripheral distribution of the muscular activity. The cerebral discharges were found to emanate from two generators. One, transversely oriented and extending

pletely pathological character encountered in the study of cerebral activity; it is not in any sense diagnostic of any particular disease state and is found in varying degrees in all types of epilepsy, particularly when there are signs or symptoms of disturbance in the subcortical nuclei.

Extreme regularity of electrical discharge and uniformity of pattern are not found in conditions where only the cortex is affected by disease; nor, of course, are these features characteristic of infancy or of deep sleep, when the more irregular slow rhythms are as common as they are in relation to cortical pathology.

Study of the time relations between the cerebral and muscular discharges showed that during a jerk-discharge the synchronous electromyograms always began during

the first electro-negative phase in the temporal lobes, and reached their maximum during the following positivity.

PROGRESS. Myoclonic spasms began in April, 1951, first involving mainly the legs and later the right arm and left leg. She developed slight facial weakness on the right side.

About May 20, 1951, her speech became slurred, and she became incontinent of urine and faeces. She lay with the limbs permanently flexed, and activity was hampered by the frequent myoclonic spasms. Treatment with artane, 2 mg. daily, was without effect on the myoclonic spasms, which became more frequent and more violent and were accompanied by oculogyric crises.

air sinuses, pituitary fossa and middle ears.

A 5 cm. cube of brain tissue was removed from the right parieto-occipital region with sterile precautions and sent to Dr. Weston Hurst for investigation for virus.

A full necropsy was performed 24 hours later by Dr. A. D. Fraser, who found that death had been due to acute bronchopneumonia, associated with marked toxic changes in myocardium, liver, spleen and kidneys.

As a result of his investigations, Dr. Weston Hurst reported that ' wholly negative ' results were obtained on animal inoculation.

PATHOLOGICAL REPORT (Dr. M. C. W. Dodgson). Except for some increased prominence of the cerebral subcortical vessels, no macroscopical changes were noted

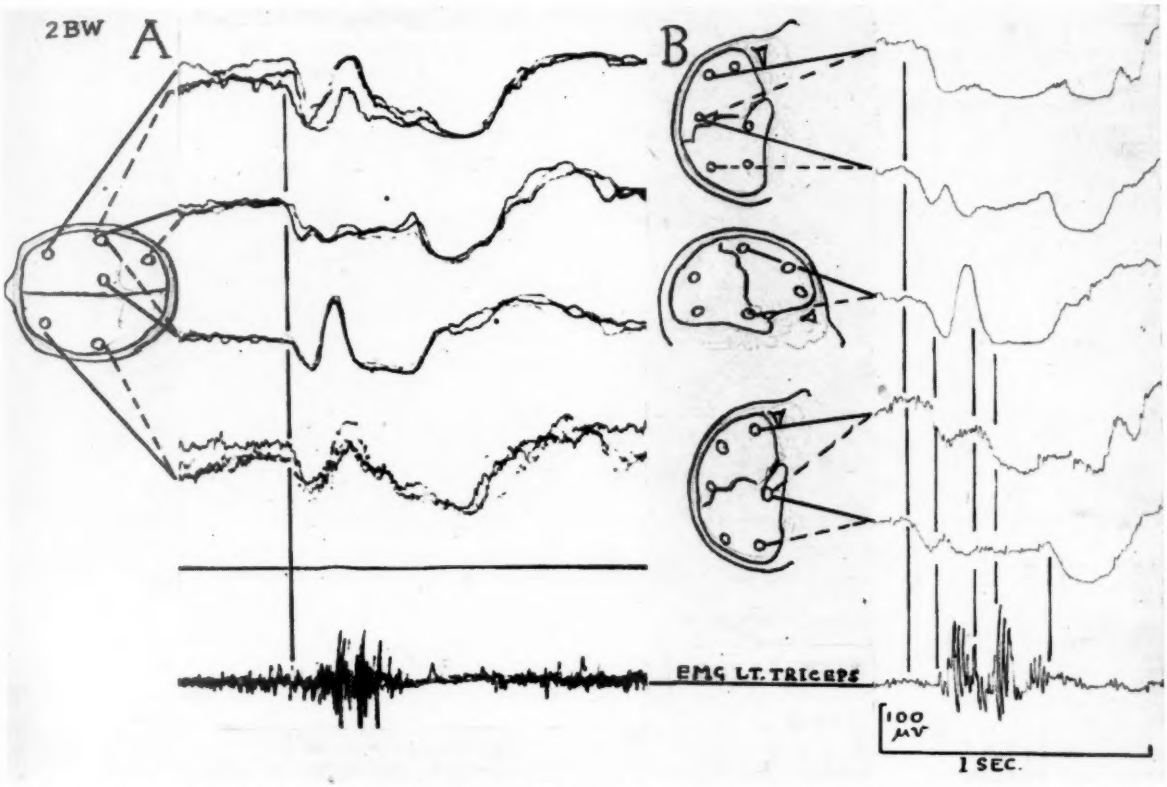

FIG. 2.—A. Print from three records at the cerebral discharge superimposed to demonstrate the unusual constancy of its wave-form and the constant grouping of the muscle discharge. B. The distribution of the various components in the right hemisphere and their relation to muscle discharge.

Towards the middle of June, 1951, the spasms were distinctly less intense but her condition began to deteriorate. She grew progressively more emaciated and latterly developed bilateral facial paralysis and bilateral ptosis.

On July 7, 1951, she was comatose and she died on July 19, 1951.

NECROPSY. The brain was removed two hours after death by Professor T. F. Hewer. Apart from a localized, pale grey exudate over the vertex, more on the left side than on the right, alongside the great veins, no changes were detected in the skull, meninges, brain, venous and

externally or on sectioning the brain.

Blocks were taken from frontal cortex and from the pons for paraffin embedding; for frozen sections from the main cortical areas, the thalamus and the pons, and for celloidin embedding from all areas.

In addition to the usual staining methods, Lendrum's phloxine tartrazine stain for inclusion bodies was used on the paraffin and celloidin sections.

Widespread histological lesions were encountered throughout the grey matter, where many of the larger nerve cells, picked out apparently at random, exhibited severe changes and were surrounded by glial cells.

In the cerebral cortex occasional pyramidal cells in the third, fifth and sixth layers displayed shrinkage and chromatophilia of the cytoplasm, although formed Nissl substance was absent; even, dark staining of the nucleus, which no longer possessed a chromatin framework; and swelling, blurring of outline and loss of refractility of the nucleolus. The nuclei of a small proportion of these damaged cells were shown to contain small vacuole-like, faintly phloxinophilic inclusions in preparations stained by Lendrum's method.

The surrounding interstitial cells were predominantly microglial, although small round cells and occasional plasma cells were also seen (Fig. 3). Similar glial nodules also surrounded capillaries, in which no central nerve cells were visible. A single typical example of this type of lesion was found in the posterior columns of the cervical cord. There were occasional perivascular cellular infiltrations in the cortex, and many of the capillary walls, especially in the neighbourhood of glial nodules, were more than usually cellular, as a result either of endothelial cell or microglial proliferation.

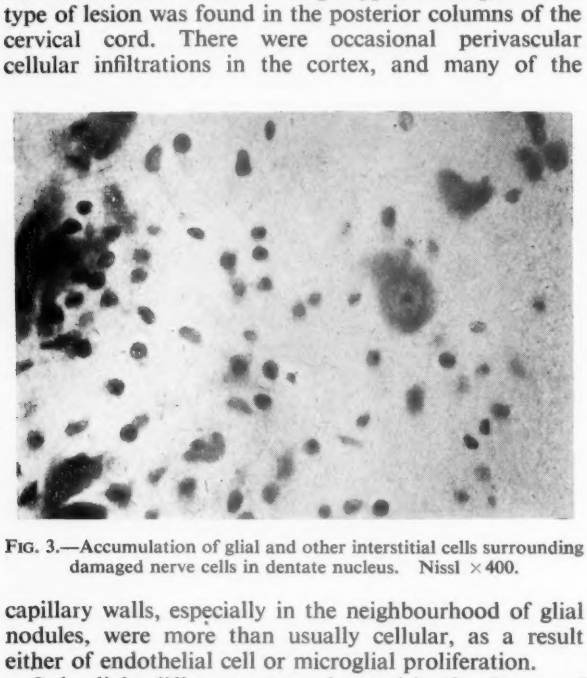

FIG. 3.—Accumulation of glial and other interstitial cells surrounding damaged nerve cells in dentate nucleus. Nissl ×400.

Only slight differences were detected in the degree of involvement of the various parts of the cortex; of all sites, the occipital region appeared to be the least heavily implicated and the temporal cortex the greatest. The larger cells in the pyriform cortex, and particularly the pyramidal cell layer of the cornu ammonis, exhibited examples of the change described above. None of the Betz cells were involved in the severe cell change or showed inclusions, although they were all in a state of chromatolysis.

Although practically every subcortical centre of grey matter was to some extent involved, the severest changes were seen in the dorsal part of the thalamus, not anatomically confined to any particular nucleus, and in the nuclei pontis. In both these situations there was a generalized astrocytic and microglial gliosis of grey matter and perivascular collections of round cells (Fig. 4).

No changes were noted in the caudate nucleus and putamen, although a few damaged nerve cells surrounded by glial clusters were seen in the globus pallidus and subthalamic nucleus. The hypothalamic region and mamillary bodies, as well as the red nucleus, periaqueductal grey matter, oculomotor and rectal nuclei, were only lightly involved. The amygdaloid complex and the substantia nigra, on the other hand, showed rather more frequent examples of severe nerve cell damage, although the latter was not nearly so badly affected as the nuclei pontis.

The reticular substance and the cranial nerve nuclei of the pons and medulla, particularly the facial, showed occasional damaged cells. In the inferior olivary nucleus there was a uniform shrinkage and increased cytoplasmic chromatophilia of the nerve cells, although only a few were surrounded by glial clusters. On the other hand, the dentate nucleus, whose cells were not in this pyknotic state, showed more frequent examples of severe nerve cell change. Elsewhere in the cerebellum there were no departures from normality, the Purkinje cells, molecular and granular layers, and central white matter exhibiting no changes. The anterior horn cells in the cervical cord appeared shrunken and contained unusually compact Nissl substance, although no examples of severe nerve cell change were observed.

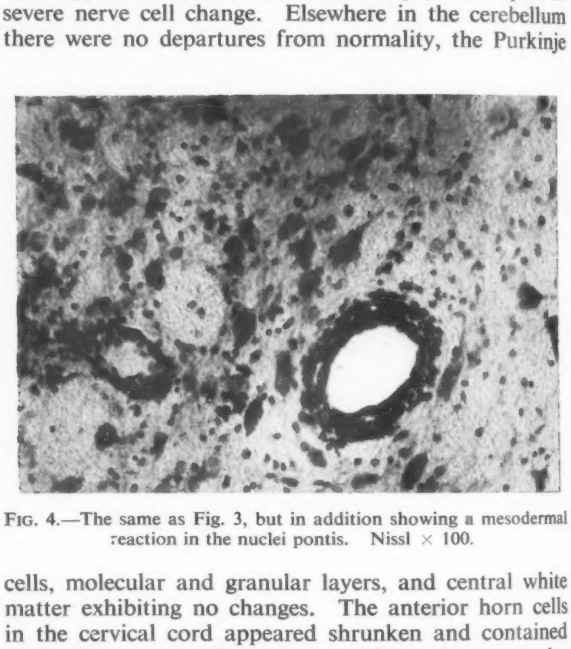

FIG. 4.—The same as Fig. 3, but in addition showing a mesodermal reaction in the nuclei pontis. Nissl × 100.

There was an obvious increase in the density of glial cell nuclei in the white matter immediately below the cortex of all regions in the cerebral hemispheres, accompanied by an increased cellularity of vessel walls, although there were no perviascular infiltrations.

In Holzer preparations it was possible to demonstrate a fine glial fibrosis, which did not, however, extend into the depths of the centrum ovale, but was confined approximately to the U-fibre zone. No evidence of myelin breakdown could be detected. Apart from these relatively insignificant changes, no other alterations in white matter were encountered, either in the cerebrum or at lower levels.

Case 2. M.G., a previously healthy child aged 6 years, was admitted to hospital on June 15, 1951. There was a history of two convulsions at the age of 2 years, associated with teething. She was the youngest of seven children and they and both parents were all alive

and well. There was no history of contact with infection of any kind before the onset of the illness.

The first symptoms began 12 to 15 months before admission, with attacks of coarse tremor occurring at night just as she was falling asleep. During the attack the child would cry out and stare vacantly, but did not appear to lose consciousness. The attacks recurred for two or three consecutive nights every two or three months. There had been one of these attacks 10 days before admission.

Four days before admission the child fell downstairs, without apparent injury, but since the fall there had been continued jerking movements and marked intention tremor affecting mainly the left arm. There had been ataxia with a tendency to fall backwards. Speech was normal, but the child was talking continually and at times did not appear to recognize people. At night she was noisy and had hallucinations.

She had attended school up to the day of admission to hospital, but study of the school books showed steady deterioration for several weeks.

For the past week there had been some incontinence of urine by day and night, and the mother had noticed behaviour changes; the child had become spiteful and a bad mixer. Previously she had always dressed herself, but for the past few days she had been unable to do so. The night before admission she complained of frontal headache. There had been no vomiting.

On examination the temperature was 98° F., the pulse 80/min. and respirations 24/min.

She was a thin child with somewhat immobile facies. She was irritable and uncooperative and reluctant to talk, though speech was normal but toneless. Her behaviour was rational and there was no impairment of vision or hearing. There was slight ataxia on walking and she showed a tendency to fall backwards. She was unable to sit for long without support. Power in the limbs was normal and equal on both sides.

There was a fine tremor of the left arm, accentuated by voluntary movements into clonic spasms.

The cranial nerves were normal. The pupils reacted to light and to accommodation and there was nystagmus to the right. The fundi were normal. Tendon reflexes were present, but brisk. There was no neck rigidity and Kernig's sign was negative. Sensation was normal.

Lumbar puncture gave a pressure of 300+ mm., and the fluid was clear and colourless with 3 cells per c.mm., chlorides 730 mg./100 ml., protein 60 mg./100 ml., a slight increase in globulin and 79 mg. sugar per 100 ml. The fluid was sterile on culture. The Lange curve was 555432000.

The Wassermann reaction was negative.

There were 17,000 leucocytes per c.mm. of blood (polymorphs 65%, lymphocytes 32%, monocytes 3%).

A radiograph of the skull was normal.

ELECTRO-ENCEPHALOGRAPHY. Records were taken on June 16, 1951, using the same methods as for Case 1. The principal feature was a large (500 microvolt) delta rhythm in both occipital lobes. This extended into the temporal region on the left side. The analysis was complex and variable; the most regular peaks were at 2 and 3 c/s and there was also a theta component at 6 c/s which was augmented by closing the eyes. In the temporal region there was a small persistent component at 14 c/s. The delta activity was augmented on the right side by closing the eyes, but with the eyes open tended to focus in the left occipital region. The alpha rhythms were small and intermittent with frequencies from 7 to 8 c/s. The patient was alternately agitated and somnolent; while sleeping a very large ' K complex ' could be evoked by a sudden sound. Photic stimulation had no unusual effects.

The complex analysis of the slow activity suggested that it was associated with a cortical disturbance, but the rhythm of the slower components, their responsiveness to stimulation and their correlation with somnolence suggested a deeper disturbance also. The greater responsiveness of the delta activity on the right side suggested that the subcortical anomaly might be mainly in the brain stem and structures around the third ventricle associated with the right occipito-parietal region. Conversely the persistence of the more irregular slow rhythms on the left side suggested the presence of a cortical disturbance in the left occipital lobe (Figs. 5 and 6).

PROGRESS. Deterioration was rapid. For the first few days she was reluctant to speak, but understood and responded to requests. At night she was noisy with visual and auditory hallucinations. She became gradually more drowsy and developed typical Parkinsonian facies and rigidity. She was unable to sit without support and movements were slow and the tremor increased in intensity. After a week she began to have constant coarse jerking spasms of the left arm and leg and there was marked neck rigidity. This progressed until the child was lying in gross opisthotonus with continual torsion spasms of the left side of the body and oculogyric crises. She remained afebrile and lucid with full comprehension, but executive ability was greatly hampered by spasms and rigidity. She took fluid and diet well and had no difficulty in swallowing till a few days before death.

Treatment with artane, 2 mg. daily, had no effect on the rigidity, and heavy sedation with soluble phenobarbitone, gr. 1 four-hourly, was necessary to control the spasms and to prevent the child injuring herself.

Four days before death the opisthotonus decreased and she became comatose, but was still able to recognize her parents and to take fluids. She developed multiple bedsores, some of which became infected, and ran an irregular fever up to 103° F. She developed a fine generalized erythematous eruption, thought to be a sweat rash.

Terminal respiratory infection occurred and she died in hyperpyrexia (106° F.) on July 12, 1951.

NECROPSY. A necropsy was performed by Dr. N. J. Brown 19 hours after death. The principle pathological changes were acute bronchopneumonia, accompanied by a dry pleurisy on the right side and by patchy areas of basal collapse in both lungs. There was a slight excess of clear fluid in the pericardium. The brain weighed 1,170 g. There was some flattening of cerebral

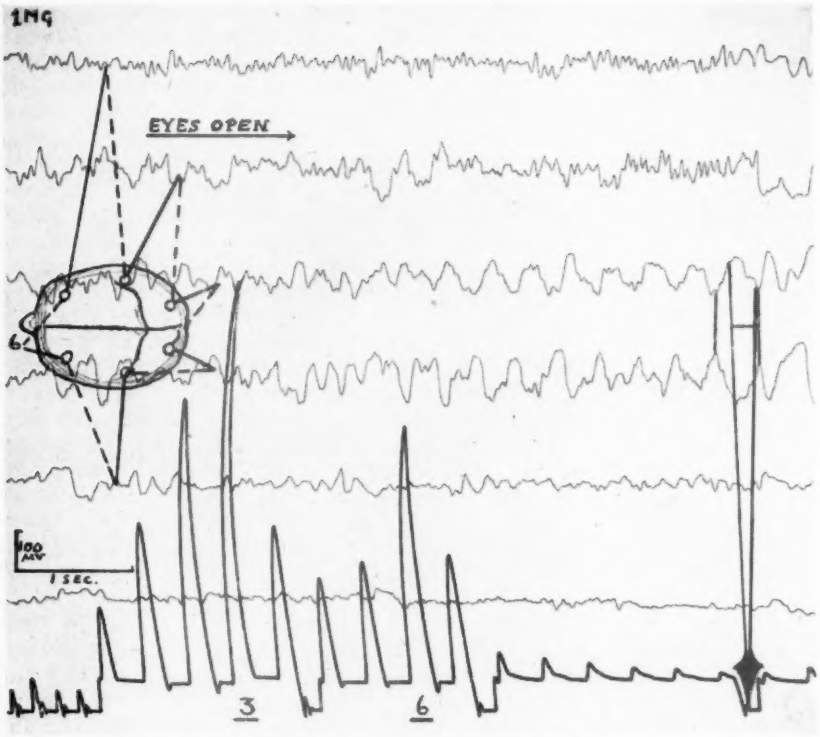

FIG. 5.—E.E.G. taken during an alert phase showing the left occipital delta rhythm with components at 3 and 6 c/s and the faster rhythms at 14 and 18 c/s from the opposite side. The analysis is of those components which were out of phase in channels 3 and 4.

convolutions and obliteration of sulci, and there was a pressure cone in the foramen magnum.

As in Case 1 a cube weighing approximately 50 g. was removed from the right cerebral hemisphere with sterile precautions and sent to Dr. Weston Hurst for virus investigation. The results in this case also were wholly negative.

PATHOLOGICAL REPORT (Dr. J. G. Greenfield). The brain stem had been divided in the mid-sagittal plane and the hemispheres separated along the line of the corpus callosum and the third ventricle.

There was no definite sign of disease on naked eye examination.

Pieces from various areas were embedded in paraffin after 10 days' mordanting in saturated $HgCl_2$ at Professor Lendrum's suggestion, and stained by Lendrum's phloxine tartrazine method, as well as by haematoxylin, van Gieson stain and phosphotungstic acid haematoxylin (Mallory). Frozen sections were also made from the parieto-occipital region and fronto-parietal vertical region of the brain and stained by Scharlach R and haemalum. The latter showed an area of partial sudanophilic myelin degeneration in the white matter under the parieto-occipital fissure in the form of loosely packed fine spicules and granules of lipid, most of which were anisotropic. They were mostly intracellular but some still remained free, lying among myelin sheaths which were sparser and more beaded than normal. In the other areas examined the myelin appeared normal. The optic nerves, chiasma and anterior parts of the optic tracts also were normal, as were the optic radiations.

In paraffin sections the medulla and cerebellum showed little abnormality. There was perhaps slight microglial excess in the inferior olives but no glial stars were seen here. In the pons the nuclei pontis showed more definite microglial excess and some degenerative changes in nerve cells but no glial stars, perivascular infiltration or inclusion bodies.

The midbrain seemed entirely normal. In view of the terminal Parkinsonian attitude special attention was paid to the substantia nigra, but nothing abnormal was seen in its cells. In the external geniculate body there was a slight excess of microglia, almost amounting to glial stars in places. No perivascular infiltration was seen here. Some nerve cells were shrunken and their nucleus was pushed to the side but none containing inclusion bodies were seen.

The optic thalamus showed a similar appearance, general slight excess of microglia and occasional degenerated neurons, and here an occasional vessel ringed with lymphocytes. No abnormality was seen in the corpus striatum including the globus pallidus.

Very little abnormality was seen in the pre-frontal, pre- and post-central, hippocampal and inferior temporal and fronto-mesial areas of cortex. An occasional vessel had plasma cells and lymphocytes in its wall, rather more commonly in the subcortical white matter than in the cortex, and a patchy excess of microglia and a few paired astrocyte nuclei were seen in the cortex. In all these areas, apart from an occasional infiltrated vessel, the changes were so slight that it would have been almost impossible to make a diagnosis of encephalitis and certainly impossible to decide its type from the histological appearances.

In sections near the parieto-occipital fissure and through the occipital lobe and the posterior horn of the lateral ventricle much more definite inflammatory changes were found, many nerve cells containing typical intranuclear and intra-cytoplasmic inclusions. The inflammatory reactions in the cortex included considerable microglial excess with formation of glial nodules, multiplication of astrocyte nuclei, which showed pairs and fours; in some places there was also swelling of the cell body, but no formation of neuroglial fibres was seen (Figs. 7, 8 and 9).

FIG. 6.—E.E.G. taken during drowsy state showing the widespread slow complex evoked by a sound stimulus superimposed on the slow and fast activity. The distribution of the evoked response is not the same as that of the persistent discharges. Electrodes, gain, and time scale as in Fig. 5.

Round many vessels there was a single layer of plasma cells and a few plasma cells were seen loose in the tissues.

The nerve cells, especially the pyramidal cells of the third, fifth and sixth layers, were, in the most damaged areas, so degenerated that they were difficult to distinguish. In several places, but not always in the most severely inflamed areas, neurons containing inclusions, both intranuclear and cytoplasmic, were so numerous that at least one could be seen in almost every oil immersion field. The inclusions were very typical: those in the nucleus varied from small bodies, one-third of the diameter of the nucleus, to bodies which filled the nucleus entirely leaving only a zone of chromatin granules round them; the smaller bodies were surrounded by a clear halo. All were hyaline and non-granular. The cytoplasmic inclusions varied from small, rounded or oval, brilliantly phloxinophil bodies, to crescentic masses usually staining orange with Lendrum's method lying beside the nucleus and representing the only visible cytoplasm. All grades between these extremes were seen.

Usually cells with such flocculent cytoplasmic inclusions showed a fairly large nuclear inclusion also,

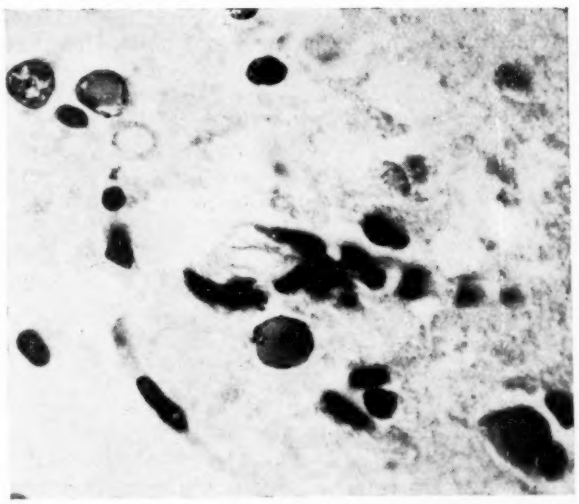

FIG. 7.—Occipital cortex: three nerve cells are seen with intranuclear inclusions. In that to the left a clear halo is seen between the inclusion body and the nuclear membrane. In the nucleus to the right the intranuclear body which fills the nucleus stains more deeply with phloxine than in the other two cells. Lendrum's phloxine-tartrazine stain ×650.

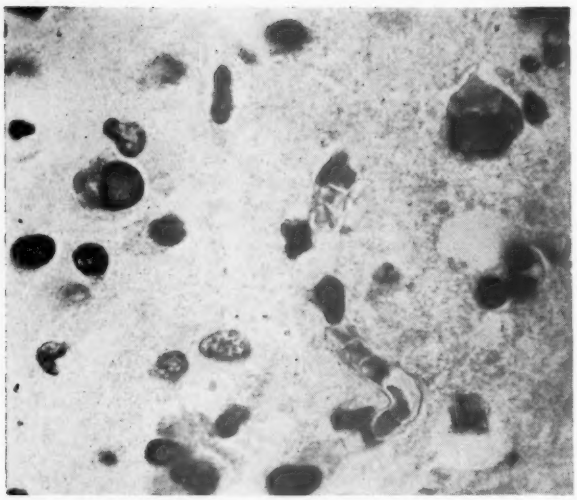

FIG. 8.—Occipital cortex: two nerve cells are seen in a state of severe degeneration with both nuclear and cytoplasmic inclusion bodies. The latter appear as flocculent, pale-staining material. Lendrum's phloxine-tartrazine stain. ×650.

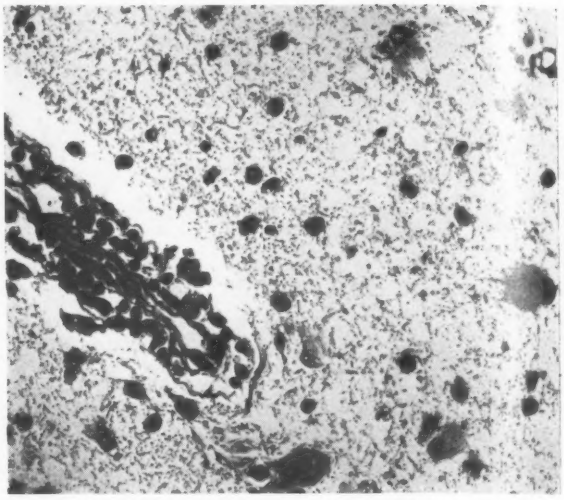

FIG. 9.—Occipital subcortical white matter showing lymphocytic infiltration of the wall of a small vessel and swelling of astrocytes. Iron haematoxylin and van Gieson stains. ×350.

but the size of the latter bore little relationship to the degree of cytoplasmic degeneration, except that cytoplasmic degeneration always accompanied an inclusion which filled the nucleus entirely.

In areas showing many such inclusion bodies an occasional cell could be seen with a rounded nucleus, rather larger and less chromophilic than that of a plasma cell, and with a large cell body filled with phloxinophilic granules from 1 to 2 μ in diameter. These cells were too sparse for their nature to be studied further. They were not recognized in sections stained by other methods.

In the occipital white matter underlying the more inflamed areas of cortex there was considerable loss of myelin, swelling of the nucleus and cytoplasm of astrocytes with fibrous gliosis and perivascular infiltration. Many of the oligodendrocytes had a clear, more or less phloxinophilic, central area in their nuclei, and a few of these cells showed a small tag of cytoplasm. These clear areas appeared to be of the same nature as the intranuclear inclusions in the nerve cells (Figs. 7, 8 and 9).

Discussion

Clinical and Pathological Findings. The principal findings in many of the cases hitherto recorded are summarized in Table 1.

It is remarkable how many cases have shown as an early symptom a deterioration in school or other work which is well shown by drawings done by our second patient (Figs. 10 and 11).

It is also striking how many patients have been found wandering in an apathetic state, and their poverty of speech is extremely striking. The facial appearance alters in these children, and this is shown by the photographs of Case 1 which show a lack of emotional expression and a somewhat plastic smile (Figs. 12 and 13).

We feel that this disease is probably a new entity and that the older neurologists could not have missed such a clinical picture. Its aetiology is entirely unknown, but it has been presumed, because of the finding of inclusion bodies, that it may be due to an unknown virus. Every attempt was made in our cases to discover an aetiological factor. The first child had had an insect bite of some severity about a year before death, but we have no evidence that the disease could be due to this and animal inoculation has been disappointing. There is no evidence that one disease is related to the herpes simplex virus, which is known to produce an encephalitis with inclusion bodies, and although material from both our cases reached Dr. Weston Hurst, he was unable to deduce anything from animal inoculation. This has been the experience of other workers.

The differential diagnosis is mainly from chorea, and the death of one patient who died recently in Wales, was thought, until death, to be due to a severe form of chorea. The electro-encephalographic changes eventually shown in most cases are, of course, entirely different from those of chorea.

Many cases have been admitted to neurosurgical units with the mistaken diagnosis of a tumour or of a subdural haematoma, and careful clinical investigations usually rule out a space-occupying lesion. Generalized neurosyphilis produced a very similar clinical picture to these sub-acute

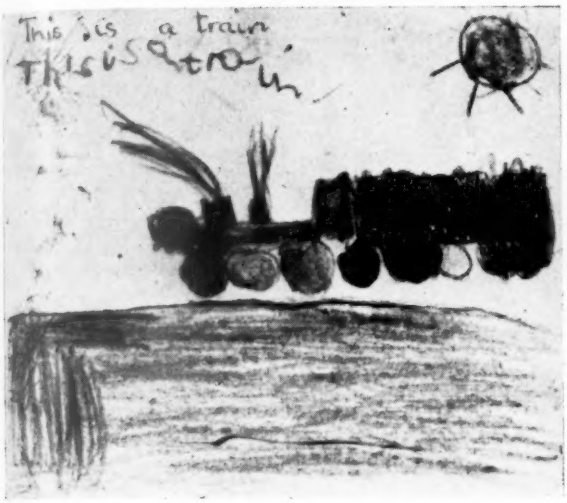

FIG. 10.—Normal drawing of train for her age done early in April, 1951.

FIG. 11.—Gross deterioration in drawing on being asked to draw same subject on June 14, 1951.

encephalitides in a case recently under the care of Dr. Spillane.

Our second case is of particular interest on account of the very localized incidence of inflammatory and degenerative changes and the relative absence of damage to the pontine nuclei, which most cases seen by Dr. Greenfield have previously shown. This local characteristic of the lesion may be associated with the short duration of the clinical symptoms, and the localization of the lesion to the occipital lobe, shown pathologically and by the electro-encephalograms, may have some bearing on the clinical symptom of visual hallucinations with which this child presented.

It is thought that the nocturnal attacks, which came on occasionally during the 12 months before coming to hospital, were epileptic attacks and not necessarily associated with the disease, although one or two cases recorded in the literature have had a long history of epilepsy before the development of the encephalitis.

In the first case the duration of the illness was of average length, six to nine months, and the histological changes were in every way typical. The mildness of the inflammatory reaction may be correlated with the absence of changes in the cerebrospinal fluid, and the lesions were concentrated in the dorsal region of the thalamus and in the nuclei of the pons. The cells of the substantia nigra, which bears the greatest brunt in encephalitis lethargica, were relatively unharmed.

Two children have recently come under our care who showed a very suggestive clinical picture of this disease with mental deterioration, clumsiness of movement and changes of tone in the limbs, but under observation have improved and returned to normality, and, although the electro-encephalographic changes were not characteristic of this disease, the clinical picture was strikingly like sub-acute encephalitis for two to three months. We have a strong impression, which, however, cannot be proved, that certain of these cases may not end fatally and may recover and it would be interesting to know whether other observers have considered this possibility.

The electro-encephalographic recordings were interpreted as a disturbance of cerebral inhibition.

Electrical Findings. The electrical observations threw no light on the aetiology of the condition but

FIG. 12.

FIG. 13.

FIG. 12.—Case 1. One year before onset of symptoms. Note normal facial appearance.

FIG. 13.—Case 1. Three months after onset of earliest symptoms. Note change in facial appearance.

TABLE 1
PRINCIPAL FINDINGS IN SOME CASES PREVIOUSLY RECORDED

Author	Age (in years) and Sex	Symptoms at Onset	Clinical Features	Duration	C.S.F.	Intra-nuclear Bodies	Result of Animal Inoculation	Further Observations
Dawson (1934) 1	M.16	Reversal of sleep rhythm; abnormal behaviour; hallucinations	Rigidity; myoclonus; cachexia	Unrecorded but over a year	14 cells, otherwise normal	Yes	Negative	A labial herpes recorded
Dawson (1934) 2	F.5	Hallucinations	Loss of ability to speak; apathy; inability to control muscles; pipe-stem rigidity; pyrexia; myoclonus; cachexia	4 months	Normal	Yes	Negative	Maculo-papular eruption, blood eosinophilia
Van Bogaert (1945) 1	M.3	Mental deterioration	Myoclonus; gradually increasing rigidity; wasting	3 months	Normal	No	Not performed	—
Van Bogaert (1945) 2	M.14	Messy eating; loss of emotions; stupor; indifference to surroundings	Myoclonus; tendency to bite everything; aphasia; apraxia; cachexia	3 months	Normal	No	Not performed	Allergic family history; measles at age of 5½
Rosanoff (1947) 1	F.6	Lost herself in streets; loss of motor control; tendency to fall	Tended to bite everything; increased tone in the legs; no myoclonus; cachexia	9 months	Normal	No	Not performed	—
Rosanoff (1947) 2	M.9	Lapses of consciousness; falling to the floor, unable to carry out errands	Meaningless facies; right extensor plantar; apraxia; cachexia, no myoclonus	4 months	Paretic Lange curve	No	Not performed	—
Malamud, Haymaker and Pinkerton (1950) 1	M.17	Psychosis; apathy; disorientation	Ptosis on the left; pill-rolling tremor; cachexia; emaciation	9 months	Paretic Lange curve	Yes	Not performed	—
Malamud *et al.* (1950) 2	F.9	Irritable; deterioration in school work; frequent falls	Optic atrophy; opisthotonos; apathy; myoclonus; wasting	21 months	Normal	Yes	Not performed	—
Malamud *et al.* (1950) 3	F.10	Gradual intellectual impairment	Progressive blindness; myoclonus; wasting	7 years	Not recorded	Yes	Not performed	Degenerative lesion at the macula of the eye
Brain, Greenfield and Russell (1948) 1	M.4	Limping; loss of use of right leg; faecal incontinence	Indistinct speech; blindness; inability to sit up; no myoclonus	11 weeks	Normal	Yes	Not performed	—
Brain *et al.* (1948) 2	M.11	Forgetfulness on errands; messy eater; unsteadiness of gait; incontinent of urine	Slow of speech; left facial weakness; myoclonus; wasting	3 months	Normal	Yes	Negative	Inoculated against diphtheria
Brain *et al.* (1948) 3	F.10	Work became slovenly; unable to dress herself; speech unintelligible	Increased tone; myoclonus	9 weeks	Paretic Lange curve	Yes	Negative	Had measles

they did permit inference of the likely extent of the lesions. The cerebral cortex, in Case 1, though deeply involved in the discharges, seemed unlikely to be directly responsible for the spasmodic outbursts; its role was rather to modify and perhaps to relay the pathological discharges from deep-lying structures.

The electrical features resembled superficially those seen in certain forms of myoclonic epilepsy, but there are two differences which may turn out to be useful in distinguishing this from the other conditions; the muscle groups involved in this case were mainly—at any rate at this stage of the disease—the extensors, and the electromyograms always changed an appreciable time *after* the start of the cerebral discharge. This interval between the

TABLE I—*continued*

Author	Age (in years) and Sex	Symptoms at Onset	Clinical Features	Duration	C.S.F.	Intra-nuclear Bodies	Result of Animal Inoculation	Further Observations
Brain *et al.* (1948) 4	M.5	Stumbling and dropping things; tendency to fall; apathy	Right facial paralysis; progressive cerebral deterioration; myoclonus	3 months	No Lange curve done, otherwise normal	Yes	Not performed	—
Akelaitis and Zeldis (1942)	M.5	Sudden onset; spastic arm; stupor	Dysarthria, torsion spasm; ocular paralysis; myoclonus	9 weeks	Paretic Lange curve	Yes	Not performed	—
Greenfield (1950) 1	M.9	Dropping things	Myoclonus; bilateral facial weakness; rigidity of muscles; opisthotonus	5 months	Paretic Lange curve; raised pressure	Yes	Not performed	Rubella and cerebrospinal fever
Greenfield (1950) 2	F.9	Incontinence of urine; falling about; apathy; inability to carry out errands	Meaningless smile; myoclonus; increasing rigidity; opisthotonus	4½ months	Paretic Lange curve, otherwise normal	Yes	Not performed	—
Greenfield (1950) 3	F.11	Deterioration in school work; awkwardness in movement; becoming blind; tendency to drop things; lack of voluntary speech	Increasing coma	7½ months	Paretic Lange curve otherwise normal	Yes	Not performed	—
Greenfield (1950)	F.20	Inability to walk; lack of facial expression; incontinence	Total paralysis of all four limbs with gross rigidity; Parkinsonism	6 months	Paretic Lange curve	No	Not performed	At age of 17, vulvar warts
Corsellis (1951) 1	F.18½	Stumbling about; vacant; unable to dress or feed herself	Developed myoclonic attacks; extra pyramidal rigidity; bilateral ptosis	6 months	Paretic Lange curve; slightly raised protein	No	Not performed	Was unsteady on her feet at age of 3 and suffered from a febrile illness at 17½
Corsellis (1951) 2	F.20	Unsteadiness of legs; dementia; tended to fall over	Irregular pyrexia; stuporose; spasticity of left arm and right leg	Uncertain, possibly a year or more	Paretic Lange curve; protein raised	No	Not performed	This patient has always been of a low grade mentality
Martin, Macken and Hess (1950)	M.7	Alteration in personality; apathy; work deterioration	Myoclonic movements; fixed facial expression	6 months	Paretic Lange curve	Yes	Still under investigation. Cerebral signs in rabbits, possibly encephalitis	Whooping cough only in previous history
Clearkin and Millar (1952)	M.11½	Transient losses of consciousness; deterioration in school work	Myoclonic movements; Parkinsonian features; finally deaf and blind	4 months	Paretic Lange curve	No	Not performed	—
Our Case 1	F.11	Personality changes; unable to perform errands; went to bed with boots on; falling down	Myoclonic movements; left facial weakness	6-9 months	Normal	Yes	Negative	Severe onset three months before symptoms
Our Case 2	F.6	Deterioration in school work; tendency to fall down	Myoclonic movements; opisthotonic rigidity	2-3 months	Paretic Lange curve	Yes	Negative	Infantile convulsions

central and peripheral events was never less and often more than 0·1 seconds, suggesting that the discharge to the periphery may have been relayed through the cortical motor zone.

In myoclonus epilepsy, on the other hand, there is usually a predominance of flexor jerks giving rise to the complaint of falling or weakness, and there is little or no delay between the cerebral and muscular discharges; in some cases indeed the electromyogram regularly displays enhanced activity slightly *before* the electro-encephalogram. This has suggested that in myoclonus epilepsy the *locus morbi* is in those subcortical nuclei which project directly to the motor neurons of the spinal cord;

in this case, however, it seems more likely that the subcortical involvement was at least one stage further from the centrifugal channels.

Another question raised by these studies is whether the intimate nature of the lesion responsible for the discharge was excitatory or inhibitory. The amplitude and regularity of the electrical phenomena may at first sight suggest a frankly irritative or excitatory process, but there are several features which indicate greater complexity. In the first place, the largest cerebral component, the sharp wave, was not particularly brief or restricted; its duration was about 0·2 seconds and it could not be considered as a spike. This, together with the very extensive slow wave, the grouping of the muscle discharges and the invariable 'silent period' after the second discharge in the muscles, suggest that the pathological process may have been in the nature of an alternation between 'inhibition of inhibition' or 'depression of suppression' and inhibitory rebound. Such a process of release from control is also somewhat easier to fit in with the unusual regularity of the repetition rate and wave-form of the cerebral paroxysms.

Summary

Two cases of sub-acute encephalitis are recorded and contrasted with previous cases.

Pathological and electro-encephalographic records are discussed, and it is pointed out that the different pathological changes may be due to the very great difference in the length of the symptoms in the two cases.

It is suggested that this disease is commoner than has been imagined and every effort should be made to throw some light on its aetiology.

We are much indebted to Professor A. V. Neale for the clinical material. We also acknowledge with gratitude the assistance of Professor Hewer, Dr. Greenfield, Dr. Brown and Dr. Dodgson. For the virus studies we are indebted to Dr. E. Weston Hurst, of Imperial Chemical Industries Ltd., and for the photographs to the photographic staff of Bristol University.

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FAMILIAL HAEMOPHAGOCYTIC RETICULOSIS

BY

JAMES W. FARQUHAR and ALBERT E. CLAIREAUX

From the Departments of Child Life and Health and Pathology, University of Edinburgh

(RECEIVED FOR PUBLICATION MAY 3, 1952)

A rare and invariably fatal condition, characterized by progressive erythropenia with or without depression of the circulating granulocytes and platelets despite a highly reactive marrow, has previously been described in adults. The liver, spleen and lymph nodes are enlarged, general intoxication is profound, and there may be a relapsing fever. The course seldom exceeds a few months, and terminally jaundice and purpura may appear. Such cases have been recorded by Scott and Robb-Smith (1939), Anderson (1944) and Asher (1946).

We have no desire to complicate further the nomenclature of the reticulo-endothelial system, but we do feel that the name histiocytic medullary reticulosis suggested for this condition by Robb-Smith (1938), although aptly describing the cellular lesion in the lymph nodes, is less appropriate than haemophagocytic reticulosis when the whole disease process is considered. The latter not only indicates the system involved, but also the abnormal process and thus gives a lead to the clinical course the disease may pursue, whereas the names of other reticuloses are often eponymous or purely histological.

We have been unable to trace reports of such cases occurring in infants or children, unless those of Reese and Levy (1951) were in fact of haemophagocytic reticulosis, and wish to record two cases in siblings. The disease was rapidly fatal in both instances and in neither was a clinical diagnosis achieved before death.

Case Reports

Case 1. Robert, aged 9 weeks, was born to young and apparently healthy, unrelated, Gentile parents. Pregnancy had been normal and delivery was by forceps. The birth weight was 8 lb. 2 oz., and his condition satisfactory; he was breast-fed and thrived normally until 11 days before admission when he became apathetic, fretful and, within 48 hours, was febrile and vomiting. During the following week sickness, fever and listlessness persisted, the stools were a little loose and contained mucus, and the skin was oddly muddy or ' sunburnt '.

On admission the infant looked ill, he was febrile and had a café-au-lait pigmentation of the skin. The liver edge and the tip of the spleen were both palpable three fingerbreadths below the right and left costal margins, but lymph node enlargement was not noted. The Wassermann and Kahn tests were negative in parents and child, the urine was free from abnormal constituents and the stools were normally pigmented.

No infection could be detected clinically to explain the fever, and throat swabs, rectal swabs and a blood culture were negative. The blood cholesterol level was 125 mg.%, the alkaline phosphatase 10 King units and the thymol turbidity 2 units; the blood urea nitrogen was 9 mg.% while the total serum protein was 4·2 g.% with a normal albumin-globulin ratio. The peripheral blood on the day of admission showed a normochromic anaemia with a haemoglobin of 52% (Sahli), the haemoglobinometer having been checked by the photoelectric technique and found accurate to within 5% (100% = 13·8 g.%). Stained blood films consistently showed a high percentage of ' smear ' cells thought probably to be of lymphoid origin, but despite many careful attempts to prepare films in which the cells might be preserved for study, all were unsuccessful. Granulocytes were few, platelets deficient, and the bleeding time ranged from 16 to 27 minutes although the clotting time was normal. Fig. 1 records the progress of this case.

Red cell fragility was normal. Marrow was readily obtained by tibial puncture and showed: neutrophil polymorphs, 8%; neutrophil metamyelocytes, 9%; neutrophil myelocytes, 6%; eosinophil polymorphs, 1%; eosinophil metamyelocytes, 1%; large lymphocytes, 12%; small and intermediate lymphocytes, 52%; monocytes, 3%; 98 nucleated red cells per 100 white cells.

The infant's blood was Group O Rh negative with a negative Coombs test while the parents were O Rh positive. Radiological examination was reported as showing some periosteal elevation over both femora and humeri.

The illness ran a rapidly fatal course characterized by a remittent temperature resistant to massive doses of penicillin, progressive panhaematopenia with some nucleated red cells in the peripheral blood, and the terminal appearance of jaundice without any excess of urobilinogen in the urine. The hepatosplenomegaly persisted unchanged, and in the last few days fairly widespread skin bruising appeared. A small transfusion

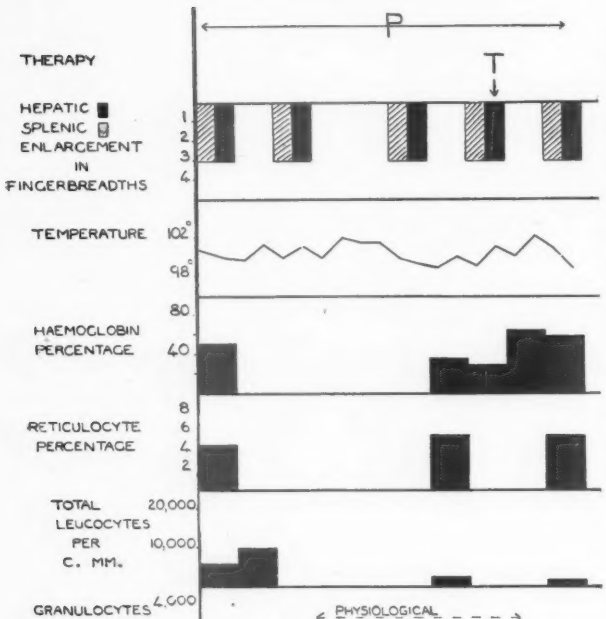

FIG. 1.—Clinical record of Case 1.

was of no value in arresting the downhill progress, and the baby died on the tenth day in hospital and the twenty-first day of his illness.

NECROPSY REPORT. The body was that of a large male child weighing 13 lb. It was very jaundiced. The abdomen was greatly distended and large ecchymoses were present.

The brain was not abnormal apart from some diffuse yellow staining of the cerebral and cerebellar cortex. In the thorax there was evidence of terminal aspiration of gastric mucus. The lungs were healthy and the heart not abnormal. The abdomen was somewhat distended and the liver large with a smooth capsule. On section the organ was a peculiar bluish green, and some yellow flecks were noted.

The spleen was greatly enlarged, firm and dark red, while section revealed congestion.

The biliary system was normal. Apart from a few petechial haemorrhages over the kidney surface, the urinary tract appeared healthy. The marrow in the mid shaft of the femur was highly reactive.

MICROSCOPICAL REPORT. The capsule of the liver was normal. The liver cells showed post-mortem change, but in addition there were areas of central and portal zone necrosis and there was widespread fatty degeneration affecting all zones of the lobules. In the necrotic areas only the outline of liver cells remained and there was some inflammatory cell infiltration. These cells were mainly lymphocytes and plasma cells but a few polymorphonuclear leucocytes were also present. The cellular infiltration was most pronounced in the portal tracts. There was considerable post-mortem invasion by bacteria so that it was difficult to assess the degree of ante-mortem necrosis.

The capsule and trabeculae of the spleen were little affected. The pulp showed severe post-mortem change. It had been intensely congested, but the majority of red cells had become lysed. The Malpighian bodies were still recognizable but they, too, had undergone post-mortem change.

The bone marrow was highly reactive. The reaction was normoblastic in character. Some post-mortem change had occurred.

Nothing of relevant importance was noted in the heart, lungs, kidneys or brain and these findings did not explain the clinical picture of a progressive panhaematopenia despite a highly reactive marrow. It was considered possible that the maturation of all elements of the marrow had been inhibited by either primary or secondary functional hypersplenism and that this influence had been effective in preventing immature cells from spilling out in greater numbers into the peripheral blood.

Case 2. Rachael was born to the same parents in the following year. Pregnancy had been uncomplicated, and delivery of the baby, who weighed 7 lb. 6 oz., was spontaneous. She appeared well at birth, was not jaundiced and fed eagerly from the breast, gaining 4 to 6 oz. weekly.

Five days before admission, when 9 weeks old, she had a few loose stools and then three days later she vomited, was listless and fretful and ' looked sunburnt '.

The vague but almost identical symptomatology, which had heralded the fatal illness of the first child, occurring at exactly the same age in weeks, disturbed the parents and they brought the baby to hospital. Preliminary examination revealed a clinical picture closely resembling that of the deceased sibling.

The infant weighed 10 lb. 6 oz., was febrile and peevish and the skin had the same sunburnt appearance. Both liver and spleen were enlarged to two fingerbreadths below the costal margin, but again lymph node enlargement was not noted. The haematological findings, the enlargement of the spleen and liver and the daily temperature, with the therapy, are recorded in Fig. 2. Once again, the differential blood film was characterized by scanty numbers of granulocytes and a varying percentage of smear cells. It was not possible to make films without damaging these cells, and although they frequently varied in inverse proportion to the granulocytes they more closely resembled the lymphoid series. Marrow was obtained with ease from the tibia repeatedly

during the illness and in more than usual abundance. The myelograms will not be reported in detail as the reports were fairly consistent and described a brisk leuco- and erythroblastic reaction, at times with a preponderance of lymphocytes. No other abnormality was noted. Red cell fragility was normal. The Wassermann and Kahn tests and the tuberculin reaction were negative. The serum cephalin cholesterol test was +++, the thymol turbidity 4 units and the serum alkaline phosphatase 20 King units %. No abnormality was noted in the total serum protein, albumin-globulin ratio, blood urea nitrogen, serum chloride, serum sodium and potassium, serum phosphorus and bilirubin levels.

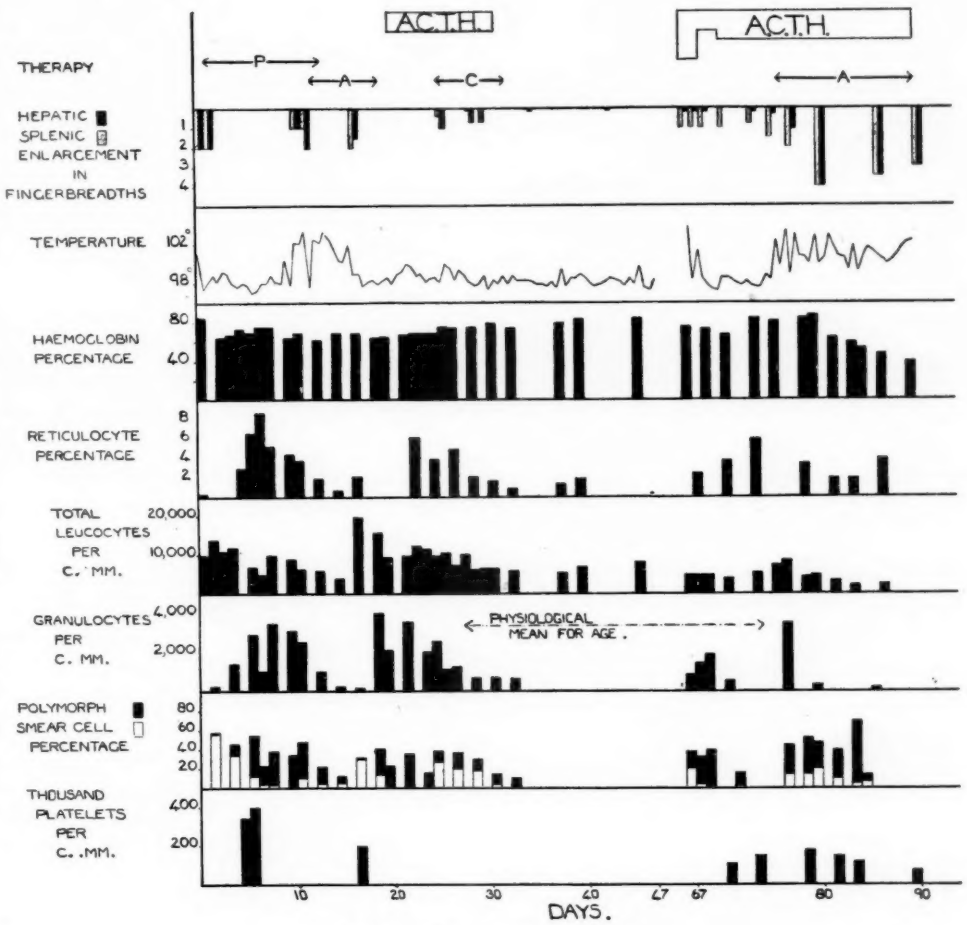

FIG. 2.—Clinical record of Case 2.

The blood group was O Rh positive, and the Coombs test was positive.

Radiological examination of the chest, abdomen and bony skeleton only served to confirm the enlargement of liver and spleen.

The baby proved to have a poor appetite and tube-feeding was at times necessary while at others the diet had to be reduced to Ringer-lactate solution on account of loose and offensive stools. The periodic bouts of pyrexia—the temperature never really settled—received treatment with penicillin, chloramphenicol or aureomycin, but without any obviously related good effect. Between the fifteenth and eighteenth days after admission the granulocytes fell to their lowest absolute level, large numbers of smear cells appeared, and the spleen, which had temporarily receded, again increased in size. The haemoglobin fell a little as did the reticulocytes although there was no consistent relationship between these two. It was decided, in view of the possibility of hypersplenism and the reputed anti-splenic action of A.C.T.H., to give this versatile substance a trial. A.C.T.H. therapy was begun on the twenty-first day in doses of 2·5 mg. six-hourly, a rapid and sustained fall in the absolute eosinophil level being achieved. Both liver and spleen receded; there was a 12% rise in the haemoglobin content, and an initial rise in the absolute level of granulocytes was followed within the period of treatment by a fall; but most striking was the general improvement which coincided with the giving of A.C.T.H. After a 10-day course (total 100 mg.) the baby remained well and regained the weight which she had lost steadily during therapy. The marrow was uninfluenced and remained richly cellular. She was discharged home 48 days after admission in the fifty-third day of her illness.

She remained reasonably well for 12 days and then during the next week she became pale and had some vomiting. She was readmitted with a high temperature, enlargement of the spleen, a low granulocyte count, and looking fretful and ill. A.C.T.H. therapy was begun at once in a dosage of 25 mg. daily, and there was an initial dramatic response enabling the dosage to be reduced to a daily intake of 10 mg. after two days. A further disturbance of the temperature, however, and a sharp

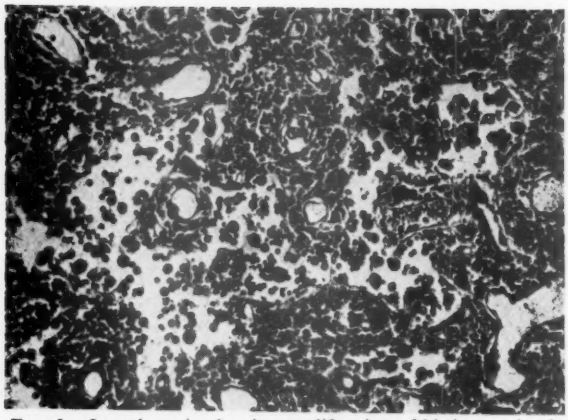

FIG. 3.—Lymph node showing proliferation of histiocytes in the sinuses. Haematoxylin and eosin. ×100.

FIG. 4.—Histiocytes in sinus of a lymph node showing phagocytosis of red cells and white cells. Haematoxylin and eosin. ×500.

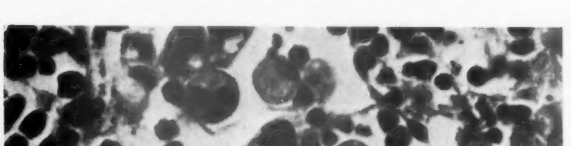

FIG. 5.—Numerous histiocytes showing haemophagocytosis in the splenic pulp. Haematoxylin and eosin. ×425.

drop in the granulocytes necessitated the addition of a further 5 mg. to the dosage. Despite this, the general condition continued to deteriorate. The baby had a high remittent temperature for which no explanation could be found; the liver and spleen rapidly enlarged, the skin became more 'sunburnt' although there was no rise in the serum bilirubin level and some purpura was noted; the haemoglobin, absolute granulocyte and platelet counts fell despite a richly reactive marrow; nucleated red cells were numerous in the peripheral blood (83 per 100 white cells), there were many polychromasic cells and a few large immature cells, which were classed as lymphocytes, appeared.

The baby died on the twenty-fourth day of her second admission in the ninety-fourth day of her illness.

NECROPSY REPORT. The body was that of a fairly well developed, but extremely pale, female infant, weighing 12 lb. 11 oz. The abdomen was greatly distended. The examination was limited to an abdominal incision.

The liver was enlarged and pale on section. Splenomegaly was present and on section the organ was dark red. The renal cortex and medulla were found to be very pale.

The mesenteric and para-aortic lymph nodes were reddish-pink and slightly enlarged. The marrow was red and reactive.

No other abnormality was noted.

MICROSCOPICAL REPORT. There was a considerable alteration in the architecture of the mesenteric lymph nodes as the result of an extensive proliferation of the littoral cells in the sinuses (Fig. 3). The follicles were small and the sinuses were packed with histiocytes and prehistiocytes, which varied in size from 10μ to 25μ. They had an oval or horseshoe-shaped nucleus and an acidophil cytoplasm. They were actively phagocytic and many contained one or more red cells, lymphocytes and even polymorphonuclear leucocytes (Fig. 4). In a few cases the red cells had been destroyed and haemosiderin granules were present in the histiocytes.

The capsule and trabeculae of the spleen were normal. The pulp was intensely engorged and packed with erythrocytes. The Malphighian bodies were poorly developed. Some were very small and a number of arterioles lacked a lymphocytic sheath. In the pulp there was a great proliferation of histiocytes (Fig. 5). Many of these showed erythrophagocytosis and others contained lymphocytes and polymorphs. There was slight haemosiderosis.

The capsule of the liver was normal. The liver cells in the portal zones of the lobules showed slight fatty degeneration. There was very extensive infiltration of the portal tracts and periportal zones by histiocytes, lymphocytes, reticulum cells and plasma cells (Fig. 6). In addition there was widespread proliferation of the histiocytes throughout the liver sinusoids where they had probably arisen from Kupffer cells. The histiocytes were actively phagocytic and contained red cells, lymphocytes and polymorphs (Fig. 7).

In the kidneys focal collections of cellular infiltration were noted in the cortex around a number of glomeruli. The cells were chiefly reticulum cells and lymphocytes, but large histiocytes were also present.

Sections of lumbar vertebrae were examined. The marrow was reactive and very cellular. There was a tremendous proliferation of acidophil histiocytes. These cells showed great phagocytic activity and were ingesting red cells, lymphocytes and polymorphonuclear

leucocytes (Fig. 8). There was considerable normoblastic erythropoiesis and granulopoiesis was also in progress.

After these interesting histological findings the sections from the previous child were examined again.

ADDENDUM TO MICROSCOPICAL REPORT (CASE 1). The capsule and trabeculae of the spleen were normal. The pulp was engorged but most of the red cells had become lysed as a result of post-mortem change. The Malpighian bodies were poorly developed and rather small. A number of arterioles lacked a lymphocytic sheath. There were large numbers of acidophil histiocytes throughout the pulp and many contained lysed erythrocytes and disintegrating polymorphonuclear leucocytes.

There was considerable histiocytic proliferation in the sinuses of the lymph nodes and many of the histiocytes showed phagocytosis of red cells and polymorphs. There was much post-mortem change.

Post-mortem change in the bone marrow was severe, but numerous histiocytes could be made out and they were seen to contain red cells.

There was moderate infiltration of the interstitial tissue of the kidneys with histiocytes.

The capsule of the liver was normal. The organ had undergone considerable post-mortem change. The portal tracts showed heavy infiltration with lymphocytes and histiocytes. The liver cells in the portal zones of the lobules showed fatty degeneration. Numerous histiocytes were also present in the sinusoids.

Case 3. Although warned that further children might be similarly affected, the parents permitted another pregnancy. The mother remained well but anxious throughout, showed no evidence of Rh sensitization, and in August, 1952, a girl was born.

This infant's progress has since been followed by one of us (J.W.F.). No abnormality was noted at birth apart from an increased number of smear cells in the peripheral blood. She was thereafter examined clinically, haematologically and serologically at intervals of six weeks. Enlargement of the lymph glands was noted at two weeks but quickly resolved. The percentage of smear cells fell but did not disappear and serological examination remained negative till the age of 8 weeks. At this point a trace of cold agglutinins appeared in the blood and also 33·5% of cells, the nature of which could not be accurately defined. Dr. A. R. Macgregor reported on the film as follows:

'The large mononuclears are cells that might be small monocytes or atypical large lymphocytes. They have pale cytoplasm and a nucleus that is often distorted and flattened so that identification is difficult. Their large number is an unusual feature of the films.'

At 10 weeks the parents brought the child to hospital because of sudden marked anorexia and the mother feared that the complexion was assuming the character noted in the two affected siblings. This latter sign was doubtful and although palpable the liver was not considered to be enlarged while the spleen was not palpable. The haemoglobin had fallen somewhat and the peculiar cells in the peripheral blood persisted. More strikingly, however, the Coombs test had become undoubtedly positive. The anorexia, the falling haemoglobin, the presence of smear and other atypical cells with the finding first of cold agglutinins, and then a positive Coombs test at the eighth and tenth weeks are ominous. The case will continue to be followed and reported later should the diagnosis be confirmed.

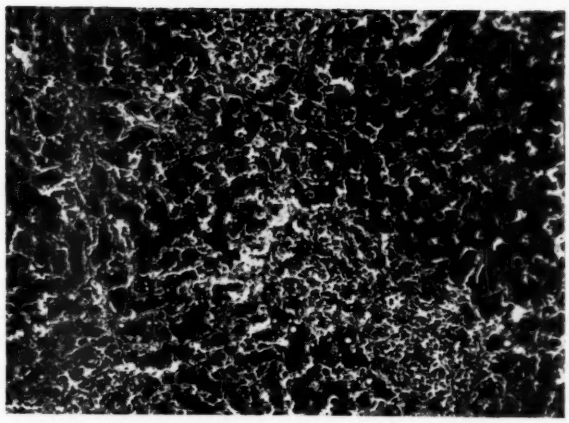

FIG. 6.—Pronounced cellular proliferation in the portal tracts of the liver. Haematoxylin and eosin. ×80.

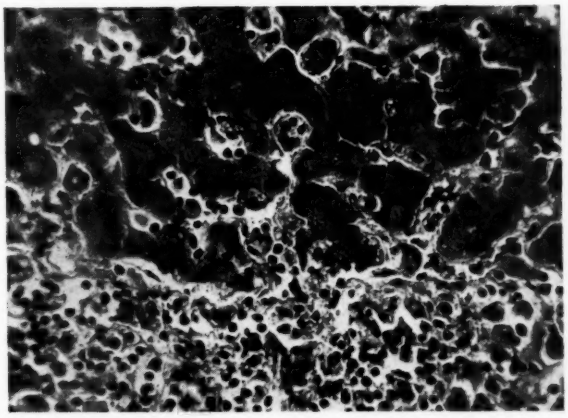

FIG. 7.—Infiltration of portal tracts with histiocytes, reticulum cells, lymphocytes and plasma cells. Histiocytes in the sinusoids show haemophagocytosis. Haematoxylin and eosin. ×280.

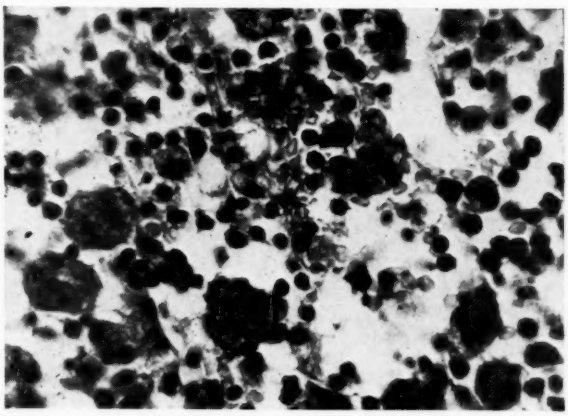

FIG. 8.—Large histiocytes in the bone marrow full of red cells and white cells. Haematoxylin and eosin. ×450.

Discussion

During the second child's illness a detailed family history of four generations was obtained, and although the families were large, few deaths had occurred in infancy and of these the cause was unknown to the available witness in two cases only. In the others death could not be suspected as being due to familial haemophagocytic reticulosis from the available history.

The positive direct Coombs test in the second infant was also made the subject of further investigation. Her blood group was O R_1 r (CDe/cde), and her father, who was O R_2 r (cDE/cde), also had a positive direct Coombs test which was confirmed at the Lister Institute. The mother was O R_1 r (CDe/cde) and no abnormal antibodies against a wide range of known blood groups (MNS, P, Lewis, Lutheran, Kell, Duffy and Kidd) could be distinguished in her blood. It was decided to follow up the paternal side of the family, and the grandfather was found to be group O R_1 R_1 (CDe/CDe) with a negative direct Coombs test. The grandmother, who was a robust woman of late middle age, was found to be group O rr (cde/cde). Her direct Coombs test was probably negative and was ruled as being so by Dr. Mourant at the Lister Institute, but Dr. Cumming noted an atypical clumping of cells, which could be dispersed by agitation, such as he had observed previously in cases of haemolytic anaemia. These findings were not explained, but it was considered feasible that the disordered reticulo-endothelial system was responsible for the abnormal antibody. The fact that the direct Coombs test had been reported as negative in the first baby was against this, but a link was provided by this strange finding between the second child and the paternal side of the family. Another interesting feature was the discrepancy between the Rh genotyping of the grandparents and their child, either the genotyping being incorrect or else there were ramifications of the family stock not incorporated in the official pedigree. This latter finding leaves open the possibility that an abnormal gene was introduced at this point.

The parents of the children were subjected to physical and haematological examination, but all that could be found was a muddy pallor of the skin in the father whose haemoglobin was estimated at the low level for a male of 86%, despite the fact that his diet was satisfactory; there was no obvious blood loss and he was an energetic and successful Association footballer. It was thought unlikely that marrow puncture would aid further in his assessment as it had not provided the clue in the children. In haemophagocytic reticulosis and in Letterer-Siwe disease there is a tremendous increase in the number of histiocytes in the bone marrow at the expense of the blood-forming cells. This histiocytic proliferation probably increases the cohesion of the marrow and renders aspiration more difficult. It was not found possible to carry out splenic puncture, lymph node biopsy, or marrow trephine.

In the children histological examination revealed lesions in the lymph nodes, spleen, liver, bone marrow and to a lesser extent in the kidneys.

The condition is a reticulosis. This takes the form chiefly of a tremendous overgrowth of histiocytes, but reticulum cells, lymphocytes and plasma cells are also found, particularly in the medulla of lymph nodes and in the portal tracts of the liver.

Once the pathology is known the clinical picture is readily understood. In response to the histiocytic phagocytosis of the blood cells in lymph nodes, marrow, liver and spleen the marrow attempts to compensate by brisk haematopoiesis. It may be that the abnormal process is present at birth, but that at that stage the marrow and extra-medullary centres are capable of holding the balance. By 9 weeks of age, however, in both cases the destructive process preponderated although there was some cyclical remission and relapse in Case 2, and terminally in both cases the marrow was unable to cope with the progressive destruction and progressive panhaemotopenia. Estren and Dameshek (1947) and Dameshek and Estren (1950) believe that the spleen normally exerts an influence on the marrow designed to prevent the escape of immature cells into the peripheral blood, and when this is excessive inhibition of the marrow may follow with a progressive deficiency of one or more cellular elements in the blood stream. Such functional hypersplenism may be not only primary but secondary to other disorders causing splenomegaly. Should this be so, then the destructive process in haemophagocytic reticulosis alone may not be responsible for the full clinical picture, but the marrow, although apparently hyperplastic may be partially arrested and its capacity to compensate hampered. If it were to have been removed in these cases more immature cells of both the red and white series might have been released into the peripheral blood.

In the second child there appeared to have been at least one partial remission possibly associated with the giving of A.C.T.H. From the graphical records (Figs. 1 and 2) it is not possible to correlate closely the variations in hepatosplenomegaly with the peripheral blood findings, because the former is but a measure of the destructive process and gives no indication of the compensatory haematopoiesis.

The jaundice in the first case was probably partly

haemolytic and partly due to hepatic dysfunction. Even when the serum bilirubin level was normal, each case presented a peculiar sunburnt appearance of the skin which could not be explained as either racial pigment or due to exposure to sunlight.

The terminal skin petechiae undoubtedly represented the active phagocytosis of platelets and resultant thrombocytopenia.

Letterer-Siwe's disease has become synonymous with non-lipoid reticulosis and reticuloendotheliosis. Haemophagocytic reticulosis is a non-lipoid reticulosis occurring in young infants but it differs in many respects from Letterer-Siwe disease. In the first place, haemophagocytic reticulosis is a familial condition. Siwe (1933) in listing his criteria for the diagnosis of non-lipoid reticuloendotheliosis states that ' the disease is neither hereditary nor familial '. Recently Reese and Levy (1951) have described a 'familial incidence of non-lipoid reticuloendotheliosis (Letterer-Siwe disease) ', but we suggest that their cases may actually have been examples of familial haemophagocytic reticulosis although the post-mortem marrow was *not* typical. As Claireaux and Lewis (1950) pointed out, the basic pathological lesion in Letterer-Siwe disease is a granuloma composed chiefly of histiocytes. In haemophagocytic reticulosis, on the other hand, the cellular infiltrations are diffuse in character and the proliferating histiocytes do not group themselves in the form of granulomata. Haemophagocytosis is not a feature of Letterer-Siwe disease and bone defects do not occur in familial haemophagocytic reticulosis.

Physiological erythrophagocytosis occurs in the sequestration and destruction of old cells by the spleen, and pathologically when the red cell is abnormal as in congenital haemolytic anaemia. It is just possible that the basic abnormality in this condition is indeed in the red cell and that reticulo-endothelial hyperplasia is a response to it, white cells and platelets being engulfed *pari passu* with the erythocytes. On the other hand, the reticulo-endothelial system may be primarily pathological as suggested in the cases of hypersplenism described by Doan and Wright (1946) and Doan (1949).

The cases of splenic haematopenia present with acute or chronic selective sequestration and destruction of red cells (Doan, Curtis and Wiseman, 1935), platelets (Wiseman, Doan and Wilson, 1940) or granulocytes (Wiseman and Doan, 1942) associated with hyperplasia of highly phagocytic reticulo-endothelial cells with or without splenic enlargement. Doan (1949) points out, however, that the spleen generally mirrors the reticulo-endothelial system as a whole and that similar phagocytes are present in the liver, marrow, lymph nodes and diffuse connective tissue. In such cases accelerated splenic destruction of one or more cellular elements of the blood is accompanied, as in haemophagocytic reticulosis, by maximum marrow hyperplasia. This hyper-instability of the spleen may be one of the primary factors in congenital haemolytic anaemia where it may be inherited as a Mendelian dominant and at other times, where direct inheritance is difficult to establish, as a recessive. This direct inheritance of abnormal reticulo-endothelial function is also apparent in our two cases.

Splenectomy has been found successful in the treatment of splenic haematopenia (Doan, 1949), but he records two cases in which it failed and where a generalized reticulo-endothelial hyperplasia and hyperphagocytosis was found in association with a reactive marrow and where the liver, lymph nodes, marrow and connective tissue participated sufficiently to render ineffective the removal of the splenic phagocytes. It may be that such cases occupy a position somewhere between the physiological and the trend toward haemophagocytic reticulosis. The latter has certainly a widespread pathology. The cause of the histiocytic proliferation is unknown and treatment is of no avail.

Summary

Two fatal cases of haemophagocytic reticulosis occurring in infancy are described in siblings. This designation is preferred for certain reasons to that of histiocytic medullary reticulosis. Interesting familial serological findings are recorded. The clinical and pathological features are correlated and the relation of this rare condition to other disorders of the reticulo-endothelial system discussed.

We wish to express our gratitude to Professor R. W. B. Ellis and Dr. A. R. Macgregor for their advice and to the former for permission to publish these cases; to Dr. R. A. Cumming, Director of the S.E. Scotland Blood Transfusion Service, for the serological findings, to the biochemistry and pathology laboratories of the Royal Edinburgh Hospital for Sick Children for the technical investigations and to the house physicians for their careful records.

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THE COMPARATIVE EFFICIENCY OF VARIOUS TECHNIQUES FOR THE DIAGNOSIS OF THREADWORM INFECTION

BY

J. M. WATSON and R. MAC KEITH

From the American University of Beirut and the Department of Child Health, Guy's Hospital, London

(RECEIVED FOR PUBLICATION JUNE 22, 1952)

When infection by threadworms is suspected it is essential before starting treatment to confirm the diagnosis by recovering ova of the parasite from the perianal skin. This is the more important since, as Lane (1944) remarks, ' no drug is yet known that is deadly to the worm yet less risky to man than is the infection ', and the clinical picture is variable and unreliable as a basis for diagnosis.

Much work has been published during the last two decades on the diagnosis of threadworm infection, and the literature contains many accounts of methods for the recovery of the ova from the patient but few of the comparative efficiency of these techniques. Indeed, heretofore, no exact methods have been devised for the accurate comparison of one technique with another, although within recent years various workers have compared the value of perianal swabbing and scraping with that of faecal examinations or have assessed the relative merits of such newer devices as the NIH (National Institute of Health of the U.S. Public Health Institute) swab, the adhesive cellophane swab and the glass pestle by repetitive examination of the same group of infested individuals. Multiplicity of techniques has given rise to confusion. We therefore decided to investigate, by controlled experiments, the relative efficiency of some recent and improved diagnostic methods, and by clinical practice to assess their relative convenience and speed. The experimental work has been carried out in the Wellcome Laboratories of Tropical Medicine and the clinical work in the wards of The Hospital for Sick Children, Great Ormond Street, London.

Two new types of anal swab were developed which were exhibited before the Royal Society of Tropical Medicine (Watson and Mac Keith, 1947a) and the Royal Society of Medicine (Watson and Mac Keith, 1947b), and are described below.

Historical Survey

Although the extra-corporeal oviposition of *Enterobius vermicularis* was known before his day, Davaine (1860) was the first to suggest searching the perianal region for the worms and their ova rather than examining the faeces, and Vix (1860) was the first to recommend the use of a probe, curette, spatula or ivory scalpel handle for this purpose. Heller (1876) proposed the examination of any piece of paper that might have been used after defaecation, a method which was later improved and developed into the T.P. (toilet paper) swab (Watson and Mac Keith, 1947).

Various types of cotton, chamois and rayon swabs, and glass, metal, wooden and celluloid scrapers were subsequently introduced but they showed little advance over the original method of Vix.

The first major improvement was made in 1933 when Hellsten suggested wiping the perianal region with a vaselined cloth and shaking up the material obtained with a mixture of water and ether which could then be centrifuged and the sediment examined for ova. Although efficient in the recovery of threadworm eggs this method was too cumbersome and time-consuming to be generally adopted. A similar technique was introduced by Kevorkova (1946) who used a moist cotton-wool swab to wipe the anal region and then placed it in a test tube partly filled with water which was vigorously shaken before removal of the swab and centrifugation. Still more recently Markey (1950) proposed an improvement on Kevorkova's method by coating the cotton-wool swab with a mixture of vaseline and wax and substituting xylol for water in the tube.

In 1937 Hall evaluated the comparative efficiency of many of the types of swabs and scrapers previously suggested and showed that they were all

unreliable. He introduced the NIH cellophane swab which rapidly gained universal approval and adoption. Jones (1938) clarified details of its use. Reardon (1938) described the artefacts in cellophane which might simulate threadworm eggs. Folan (1939) dealt with the preparation and cleaning of the swab. Boycott (1949) introduced slight modifications in the design and method of use.

Another step forward was taken in 1941 when the use of adhesive cellophane tape instead of ordinary cellophane was independently suggested by Graham and in 1942 by Jacobs. This method has been even more widely adopted than the NIH swab and modifications of it have been suggested by Von Hofe (1944), Brooke, Donaldson and Mitchell (1949) and Beaver (1949). Ebert (1949) proposed the attachment of the adhesive cellophane strip to the anal cleft covering the anus overnight so that the worms would actually oviposit on it. Hitchcock (1949) studied the occurrence of egg-like artefacts in adhesive cellophane tape and concluded that they were rare.

In 1943 Schüffner and Swellengrebel published the first description of a device entirely new in principle and design, arising out of the observation that the ova of *E. vermicularis* are always laid in clumps which might be missed by a swab or scraper. This instrument, consisting of a small glass pestle with a rough-ground end which was wetted before application, was designed to break up these clumps into a suspension so ensuring that none should be missed. The authors claimed that in clinical trials it was superior to the NIH swab.

In 1945 Petersen and Fahey proposed to simplify the process of recovering ova from the patient by pressing an ordinary microscope slide on to the perianal skin and examining it directly under the microscope.

Finally, in 1946 Watson and Mac Keith introduced the use of a moistened camel-hair brush for the collection of eggs from the perianal region (Watson and Mac Keith, 1947).

Since that date modifications of existing methods but no substantially new techniques have been introduced. One of the most useful innovations was the differentiation of living from dead ova by staining with fluorochrome acridine orange (Beckers, 1949).

Sawitz (1940), Sawitz, Odom and Lincicome (1939) and McMullen (1949) have dealt with the question of the number of negative swabs necessary to prove that a patient is not infested with threadworms. Their findings are in no way invalidated by ours.

Comparison of the relative efficiency of diagnostic methods has been confined to empirical conclusions or to the consecutive use of two devices on the same group of patients. In this way Sawitz *et al.* (1939), Sawitz (1940) and Miller and Einhorn (1944) have compared the NIH swab with faecal concentration methods; Kuitunen-Ekbaum (1942), Mazzotti and Osorio (1942 and 1945), Meneses Rubiánez and Avendaño Escalante (1949) and Jeffrey (1950) have compared the NIH swab with the glass pestle and the adhesive cellophane swab. The general consensus of opinion of these authors was that the NIH swab was greatly superior to faecal concentration methods; that the glass pestle was superior to the NIH swab; and that the adhesive cellophane swab was superior to the glass pestle.

Material and Methods

The purpose of the experiments was to determine the percentage of ova which would be picked up from the human skin and revealed by microscopic examination in the case of each of the different devices under investigation, and so to obtain figures which could be used in comparing their relative efficiency.

Since infection of experimental animals with *Enterobius vermicularis* is not possible, and since human infection could not be controlled, the ova of the rabbit threadworm, *Passalurus ambiguus*, were employed throughout the experiments. This made it easier to obtain uniform conditions for repeated series of observations than would have been the case with human threadworms.

The ova of *P. ambiguus*, although slightly larger than those of the human threadworm, are similar in shape and have the same inner lipoidal, middle chitinous and outer albuminaceous layers of the shell, and it was therefore concluded that any results obtained with them would be valid for the eggs of *E. vermicularis*.

Between the hard, dry pellets of faeces in the rectum of freshly killed rabbits were often found gravid female worms on the way to the exterior to discharge their ova. At first only these specimens were used in the tests, but unfortunately when exposed to air by the opening of the rectum many of them discharged their eggs before they could be transferred to the experimental surface and were thus useless. Later, however, it was found that if, in a heavily infected rabbit, the caecal contents were removed into a shallow basin and placed in an incubator at blood-heat, most of the worms came to the surface of the mass within a few minutes, and large females could then be picked out and allowed to oviposit on the selected area of skin. This was more satisfactory than the use of specimens from the rectum since a greater length of time elapsed between picking up the worms in the forceps and the act of oviposition.

The efficiency of the diagnostic techniques was investigated using not only dry ova but also those which had been wetted, in case the adhesiveness of the outer layer of the eggshell was reduced by wetting.

In one group of experiments gravid females were allowed to oviposit, one at a time, on the palm of the

hand. Any worm which did not oviposit voluntarily was discarded, since in immature specimens the albuminaceous outer layer of the eggshell might not have the same degree of stickiness. The diagnostic device was then applied to the area of egg-deposition, normally a circle of about one centimetre diameter, after an interval of two or three minutes to allow drying to take place.

In a second group of experiments a large number of gravid female worms were transferred to a small volume (about 5 ml.) of physiological saline and cut into very fine pieces so as to liberate the ova from the body. A suspension of eggs was thus obtained from which, after thorough shaking to ensure even distribution of the ova through the liquid, several drops were removed with a fine pipette and placed separately on microscope slides. By using the same pipette held at the same angle on each occasion, drops of uniform size were obtained. At the same time, using precisely the same technique, a series of drops was placed on marked areas along the skin of the underside of the forearm and allowed to dry. The diagnostic devices were then applied to the areas covered by the dried drops. Counts were then made of the number of ova in the control drops on the slides and the percentage of ova recovered by each device on each application could then be calculated.

Diagnostic Devices

The patients were children between the ages of 9 months and 2 years, together with a small number of adults. The purpose of the clinical investigations was to compare the relative facility with which each device could be employed in practice, the average time occupied in its use, subsequent manipulation and microscopic examination, and the degree of discomfort to the patient.

The devices employed were the NIH swab, the TP swab, the glass pestle, the adhesive cellophane or Graham swab, the direct slide and the brush. We have already described them in an earlier paper (Watson and Mac Keith, 1947).

A number of different clearing agents were tested subsequently in connexion with the TP swab, and some account of this work may not be out of place. The best results were obtained by the use of oil of wintergreen. A dilute solution of light green in clove oil stained the background green while the unstained eggs appeared yellow. Clove oil alone also produced excellent contrast, the eggs appearing yellow against a white background. Beechwood creosote was almost equally good when viewed with minimal light. Lactophenol gave a good result only with strong illumination. Glycerin at first trapped numerous air-bubbles in the paper but after standing overnight gave better contrast than any other reagent. Monnig's medium (gum arabic 60 parts, glycerin 40 parts, chloral hydrate 100 parts, thymol 1 part) was satisfactory when tinted with eosin, the ova at first remaining unstained and showing up well against the coloured paper and later becoming more deeply stained than the paper. Cedar-wood oil, xylol, benzol, liquid paraffin, chloroform and acetone were all unsatisfactory as both eggs and paper became too transparent and there was insufficient contrast. Caustic potash and soda solutions were also useless as they failed to render the paper transparent. The preparations lasted for several days without the necessity of sealing the edges of the coverslip but showed a decreasing degree of contrast between paper and eggs as the latter gradually cleared. Numerous different varieties of toilet paper were investigated but the only unsuitable one was the crinkled type, which would not lie flat on the slide. Tissue paper was found to clear exceptionally well and would have been superior to toilet paper but for the fact that it tore very easily and required more careful handling.

Experimental Results

Experiments with Dry Eggs. The results of the first series of experiments in which ovipositing female threadworms were used and the eggs allowed to dry before carrying out the test are set out in Table 1 which gives the actual number of ova recovered in each operation.

TABLE 1

NUMBERS OF OVA RECOVERED BY EACH DEVICE

Test	NIH Swab	TP Swab	Adhesive Cellophane Swab	Glass Pestle	Direct Slide	Camel Hair Brush
1	8	5	130	19	136	71
2	100	221	82	12	3	623
3	255	15	442	13	166	37
4	56	1	210	76	3	68
5	150	5	125	26	42	121
6	118	559	139	100	41	236
7	110	163	521	63	62	140
8	180	402	34	196	124	65
9	189	81	288	96	128	174
10	190	594	129	248	184	174
11	168	749	208	57	150	518
12	26	5	108	113	74	131
13	248	22	340	16	148	138
14	23	68	215	21	227	290
15	176	262	37	56	84	405
16	249	55	354	106	51	238
17	148	349	144	223	168	182
18	412	35	219	79	52	243
19	224	59	51	7	108	209
20	60	192	108	51	43	428
21	125	171	391	40	208	497
22	235	6	33	2	91	564
23	149	54	222	3	126	506
24	18	162	259	7	75	166
25	134	174	290	183	50	464
Mean	134	176	203	73	103	266

Since the NIH and TP swabs and the brushes remained in their tubes for several days before being examined, some of the ova might have become detached and be lying loose at the bottom of the tubes. Each tube was therefore washed out with water, the washing centrifuged, and the sediment examined. In only one instance (an NIH swab tube) were any ova discovered and in this case only a single egg was found. Evidently then the adhesiveness of the egg is sufficient to ensure its adherence to the collecting surface for several days even when, as in the case of the NIH and TP swabs

and the brush, that surface is not in itself sticky. Thus delay in examination of the swabs does not appreciably lessen the likelihood of finding ova if any were originally present. The other three methods depended upon the adherence of the eggs to the surface of slides which were kept flat and did not therefore suffer from the same disadvantage.

Many of the eggs picked up by the brush are not delivered to the cavity slide for examination at the first dipping. Each brush was dipped consecutively into caustic soda solution three times. The number recovered at the second and subsequent dippings is always less than that recovered the first time (see Table 2), and no doubt depends on

TABLE 2

NUMBER OF OVA RELEASED FROM THE BRUSH

Test	First Dipping	Second Dipping	Third Dipping
1	71	—	—
2	623	—	—
3	37	—	—
4	68	42	26
5	121	106	67
6	236	127	50
7	140	77	12
8	65	60	32
9	174	154	73
10	518	470	—
11	174	92	61
12	131	30	31
13	138	57	32
14	290	90	17
15	405	116	19
16	238	36	16
17	182	171	95
18	243	115	52
19	209	10	6
20	428	125	86
21	497	67	23
22	564	126	49
23	506	61	13
24	166	84	53
25	464	207	168

the lapse of time between oviposition and application of the brush, the temperature of the caustic soda solution and the degree of mechanical agitation employed. For the purposes of this study only figures obtained from the first dipping of each brush are taken into account.

In order that a valid comparison between the figures established for the six different methods might be made it was necessary to relate them to the number of ova produced by the adult female worm. *Passalurus ambiguus*, although similar in dimensions to *Enterobius vermicularis*, has larger ova and a smaller number are therefore present in the gravid female. Search of the literature revealed no estimate of this number and it was therefore assessed experimentally. The technique of Reardon (1938) was adopted, each worm being cut into four pieces in a drop of glycerin and water on a slide and the eggs extracted by teasing with mounted needles. Adult females were obtained from the rectum of the lower part of the colon of infected rabbits and killed by immersion in hot alcohol-glycerin. Counts were made on 25 specimens, the results of which are given in Table 3.

TABLE 3

NUMBER OF OVA IN GRAVID FEMALE SPECIMENS OF PASSALURUS AMBIGUUS

Specimen	Ova	Specimen	Ova
1	997	14	786
2	578	15	696
3	760	16	495
4	803	17	501
5	686	18	210
6	652	19	477
7	818	20	633
8	636	21	1,044
9	741	22	720
10	669	23	364
11	510	24	858
12	856	25	734
13	1,019		

Arithmetic mean, 690; standard deviation, 194·02; coefficient of variation, 26·7%. Calculation of t shows that out of 1,000 females one might expect to find four with over 1,200 ova, six with under 200 ova, one with under 100 ova.

However, from the point of view of relating the number of eggs picked up from a single ovipositing female by the various diagnostic devices to the number of eggs which might be expected to be found in such a specimen, it is important that the efficiency of each method should not be overestimated. The arithmetic mean, or any other measure of central tendency, may give such an overestimate in any particular instance. It was therefore decided to use, for purposes of comparison a figure of 1,000 as being the maximum number of ova in a gravid female (to the nearest round number) and to express the pick-up figures for each type of diagnostic device as percentages of this maximum possible egg-number. The final assessment figures are presented in Table 4.

In judging the reliability of six diagnostic devices three different indices derived from the raw data (Table 1) were employed, namely: (1) the arithmetic

TABLE 4

ANALYSIS OF RECOVERY OF DRY OVA FROM A SINGLE GRAVID FEMALE PASSALURUS AMBIGUUS

Device	Arithmetic Mean	Standard Deviation	Coefficient of Variation (%)	Recovery of Less than 10 Ova (%)
NIH swab ..	13·4	7·41	55	4
TP swab ..	17·6	21·95	125	25
Adhesive cellophane swab ..	20·3	12·94	64	0
Glass pestle ..	7·3	7·02	96	20
Direct slide ..	10·3	6·04	59	8
Brush ..	26·6	17·39	65	0

TABLE 5

NUMBERS OF OVA RECOVERED BY EACH DEVICE FROM DRIED DROPS OF A SALINE SUSPENSION CONTAINING 355 OVA (MEAN) PER DROP

Test	NIH Swab		TP Swab		Adhesive Cellophane Swab		Glass Pestle		Direct Slide		Brush	
1	5	(1·4%)	1	(0·3%)	154	(43·3%)	74	(20·8%)	5	(1·4%)	98	(27·6%)
2	1	(0·3%)	8	(2·3%)	277	(78·0%)	76	(21·4%)	8	(2·3%)	9	(2·5%)
3	6	(1·7%)	1	(0·3%)	201	(56·6%)	93	(26·2%)	12	(3·4%)	25	(7·0%)
4	19	(5·3%)	9	(2·5%)	237	(66·8%)	88	(25·5%)	40	(11·2%)	207	(58·4%)
5	6	(1·7%)	12	(3·4%)	103	(29·1%)	85	(24·0%)	0	—	41	(15·5%)
6	2	(0·6%)	4	(1·1%)	175	(49·0%)	49	(13·8%)	13	(3·7%)	27	(7·6%)
7	7	(2·0%)	3	(0·8%)	85	(24·0%)	102	(28·8%)	31	(8·8%)	39	(11·0%)
8	36	(10·3%)	2	(0·6%)	131	(37·2%)	86	(24·3%)	20	(5·6%)	34	(9·6%)
9	19	(5·3%)	1	(0·3%)	148	(41·7%)	73	(20·5%)	25	(7·0%)	13	(3·7%)
10	5	(1·4%)	5	(1·4%)	200	(56·3%)	72	(20·2%)	55	(15·6%)	37	(10·5%)

mean, (2) the coefficient of variation, (3) the percentage of tests in which less than 10 ova were recovered. The final assessment was based on the combined result. The arithmetic mean may be considered the least important of these values since a high mean gives no indication of the likelihood of positive cases being missed owing to an occasional low recovery value. However, when the coefficient of variation rises, the likelihood of failure to recover any eggs when few are present also rises but it is never high in any of these methods. Clumping of ova makes it impossible to estimate statistically the likelihood of this happening. From this standpoint it is clear that there is little to choose between the adhesive cellophane swab, the NIH swab, the direct slide and the brush, all of which showed a moderately low coefficient of variation and rarely or never failed to pick up at least 10 ova. The brush and the adhesive cellophane swab displayed a slight superiority over the other two methods by reason of a higher arithmetic mean. The TP swab and the pestle both showed unreliability by their high coefficient of variation and the frequency with which they failed to recover at least 10 ova, despite the fact that the former had a high mean value.

It should be noted that the variability in picking up eggs for each method is due in part to the variability in mean female egg content as shown in Table 3. The computed coefficients of variability for each method, while artificially high, should remain valid for comparative purposes.

All conclusions were complicated by the well-known fact that the eggs tended to clump together. Statistical analysis confirmed that each egg did not have an equal and independent chance of being picked up in these tests. Comparable conditions would obtain, however, in clinical practice. The high coefficient of variation shown by the pestle indicated that perhaps it does not break up the egg-clumps as effectively as Schüffner and Swellengrebel (1943) believed.

Experiments with Wetted Eggs. The results of the second series of experiments in which a standard suspension of ova in physiological saline was used are presented in Table 5.

Analysis of this table shows that the differences in recovery values for a single method are too large

TABLE 6

ANALYSIS OF RECOVERY OF WETTED OVA FROM A STANDARD DROP OF SUSPENSION AFTER DRYING

Device	Arithmetic Mean	Standard Deviation	Coefficient of Variation (%)	Recovery of Less than 10 Ova (%)
NIH swab ..	10·6	10·3	98	70
TP swab ..	4·6	3·7	80	90
Adhesive cellophane swab ..	171·1	56·4	33	0
Glass pestle ..	79·8	13·8	17	0
Direct slide ..	20·9	16·3	77	30
Brush	53·0	56·3	106	10

to be accounted for by chance. It must therefore be concluded that here also every ovum does not have an equal and independent chance of recovery; in other words, some reclumping must take place either in the suspension or when it dries on the skin.

In arriving at a final assessment the same three indices were used as in the previous series of experiments. It was concluded that although the mean recovery figure with the adhesive cellophane swab was higher, the pestle was the more consistently reliable in view of its lower coefficient of variation. The pestle, in other words, is more likely to pick up some eggs every time. Neither device ever failed to recover 10 ova. Of the remaining devices, the TP swab and the NIH swab both had a low mean recovery figure and a high coefficient of variation and frequently failed to recover 10 ova, indicating a substantial degree of unreliability, while the brush and the direct slide, although showing an almost equally high coefficient of variation, had a somewhat high recovery rate and less frequently failed to recover 10 ova. In only

one instance (a direct slide test) did any of the devices fail to pick up at least one egg.

The tubes in which the NIH and TP swabs were stored were checked as before for detached eggs by washing them out and centrifuging the washings. No ova were recovered from any of them.

The much higher figures obtained with the adhesive cellophane swab, which, having itself a sticky surface, does not depend on the adhesiveness of the outer coat of the egg for its efficiency, leads to the conclusion that wetting the eggs reduces the adhesive properties of the shell. This was not unexpected since the outer layer of the egg-shell is albuminaceous and would therefore be removed by solution on wetting the egg with water. The low degree of efficiency shown by the NIH swab, the TP swab, the direct slide and the brush is thus explained, since the adherence of the eggs to these devices depends primarily upon the intrinsic stickiness of the outer shell.

Conclusion. The experiments described show that there is little to choose from the point of view of reliability in the recovery of ova between the adhesive cellophane swab, the NIH swab, the direct slide and the brush provided that the eggs have not been wetted. When wetting has taken place, however, the adhesive cellophane swab and the glass pestle are the most reliable devices.

Since it is often the case that the perianal region is wetted before examination either by washing, by perspiration or, in the case of young children, with urine, it must be concluded that the adhesive cellophane swab is the method of choice, since it alone appears reasonably reliable in the recovery both of dry eggs and of those which have been wetted. Schüffner and Swellengrebel (1943) estimate that 99% of ova present are removed from the perianal region by even a brief wash with water. This fact makes the use of the most reliable method for the recovery of the remainder even more important.

Clinical Considerations

The experiments described in the preceding section give an estimate of the reliability of the six different diagnostic methods tested. Reliability, however, is not the only criterion for judging a method of detecting threadworm infestation. If it is to be of practical value it must be acceptable to the person who is to use it whether he is research worker, general practitioner, clinical pathologist or parent. It must be simple and quick in use. In view of the repeated applications necessary to establish freedom from infestation absence of unpleasantness to the patient is important.

According to Hall (1937) a satisfactory swab for the diagnosis of oxyuriasis should have the following characteristics: (1) It should pick up threadworm eggs dependably. (2) It should deliver them to a microscope slide dependably with the minimum of manipulation. (3) It should be easy to transport with safety from infection and without loss of eggs. (4) It should cause the patient the minimum of discomfort.

The additional qualities which, in our experience, make for practical usefulness are: (5) Simplicity, which makes for ease of handling and speed in use and is especially necessary when a parent or other member of a household is requested to carry out diagnostic tests on a suspected case. (6) Availability of materials, which makes it simpler for a practitioner who meets relatively few cases to check a clinical diagnosis.

The only one of the six methods investigated which fulfils all of these requirements is the adhesive cellophane swab. It is, however, less suitable when the patient is an adult male with abundant perianal hair.

The NIH swab has the disadvantages that it needs time for preparation, is bulky for transport, is not easy to examine, since it frequently flattens unevenly and sometimes contains egg-like artefacts, and is disagreeable to the patient since the sharp corners and prickly edges of the folded cellophane often hurt the tender perianal skin of children, especially when pruritus and scratching have led to soreness.

The glass pestle has the disadvantages of needing special construction in the first instance and of requiring cleaning by scrubbing with soap and water between successive applications. Although slightly more complicated than the other methods it has, in our experience, been easily learned and practised by patients.

The direct slide has the disadvantage of requiring a great deal of time for examination, and, since ova tend to be most numerous at the edge of the slide, they can be easily overlooked if few. Patients experience considerable discomfort from the pressure of the sharp edge of the slide on the soft perianal skin, and for this reason we found this method almost impracticable in use.

The brush is bulky in transport and the process of cleaning for further use is lengthy and tedious, involving scrubbing with soap and hot water. On the other hand the brush caused least discomfort to the patient and was the easiest to examine since the ova tend to congregate in the centre of the cavity slide so eliminating the necessity for searching.

The TP swab, while requiring time for preparation,

if made up like the NIH swab and being bulky for transport, has one unique advantage which makes it the method of choice when ointment has been applied to the perianal skin to allay pruritus. In this circumstance, which renders the other methods nugatory, the paper will not clear since it will be smeared with an opaque film of ointment, but any ova which may be embedded in it can be readily detected by the use of dark-ground illumination.

In Table 7 are given the times occupied in the process of examination of the various devices for ova. These are average figures, obtained by careful timing of several different workers over many thousands of operations. Naturally they make no allowance for inexperience. The time taken in examination is dependent in part on the presence or absence of eggs; negative preparations naturally occupy more time than positives which may often be dismissed in a few seconds. The figures given in Table 7 are for negative preparations only and therefore represent maximum times. Schüffner and Swellengrebel (1943) found that the average time taken to examine a negative NIH swab was 11 minutes whereas a negative pestle slide could be examined in two and a half minutes as against nine minutes and three and a half minutes respectively in our tests.

TABLE 7
TIME OCCUPIED IN EXAMINATION OF EACH DEVICE FOR OVA

Device	Time (minutes)
NIH swab	9
TP swab	7½
Adhesive cellophane swab	5½
Glass pestle	3½
Direct slide	6
Brush	2½

Summary

The literature relating to the diagnosis of threadworm infestation is reviewed.

An account is given of investigations made to assess the relative efficiency of six different methods for the diagnosis of threadworm infestation. Clinical considerations, based on the use of each of the methods in a large number of cases, are also discussed.

It is concluded that of the methods used, namely, the NIH swab, the TP swab, the adhesive cellophane swab, the direct slide, the glass pestle and the brush, the adhesive cellophane swab alone is reliable whether the eggs have been wetted or not and is the only one which fulfils all the requirements of a clinically satisfactory device. It should be replaced by one of the other devices when the patient is an adult male with abundant perianal hair.

The TP swab is the method of choice when ointment has been applied to the perianal skin since any ova embedded therein are revealed by examination with dark-ground illumination.

The authors wish to express their gratitude to Professor Alan Moncrieff, C.B.E., of the Institute of Child Health in the University of London, and to Brigadier J. S. K. Boyd, C.M.G., F.R.S., Director of the Wellcome Laboratories of Tropical Medicine, for the facilities accorded to them for the carrying out this work and for their advice and encouragement during its execution.

They are also indebted to Dr. Deward Waggoner, Professor of Biostatistics in the American University of Beirut, for his assistance in the statistical analysis of the experimental results and for guiding them in the formulation of the correct deductions.

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GASTRIC CYSTS OF THE MEDIASTINUM WITH A REPORT OF TWO CASES

BY

AUDREY MATHESON, GORDON CRUICKSHANK and W. J. MATHESON
From the Children's Hospital, Leicester Royal Infirmary, and Leicester Chest Unit

(RECEIVED FOR PUBLICATION JUNE 3, 1952)

The occurrence of an intra-thoracic cyst lined with gastric mucosa is a rarity, only 31 previous cases having been reported (Table 1), although a number of others lined with mixed gastric and intestinal or respiratory mucosa have been described. Their recognition, however, is important since early surgical removal is curative. If unrecognized and causing symptoms death in infancy is usual. These points are illustrated by the following two cases.

Case Reports

Case 1. Keith H. was aged 9 weeks on admission to the Children's Hospital, Leicester Royal Infirmary, on May 21, 1949, because of repeated haemoptyses.

He was the second child of healthy parents, and was born at term after a normal delivery, weighing 6½ lb. The first child had been stillborn. On discharge from the maternity hospital at 2 weeks he had a slight cold which later 'settled on his chest'. At 3½ weeks he had his first haemoptysis and this had recurred practically every day since. At 6 weeks he was admitted to another hospital where a lung abscess was suspected. An attempted bronchoscopy was unsuccessful and needling of the right lung produced no fluid. He was given a blood transfusion and transferred to the Leicester Royal Infirmary.

On examination the temperature was normal, the pulse 130, and respiration 40. The weight was 7¼ lb. (expected weight 9½ lb.). He was a wasted, pale, dyspnoeic baby, slightly cyanosed. The fingers were clubbed. The trachea was central, and no mediastinal shift was detected. The percussion note was impaired over the whole of the right hemithorax with bronchial breath sounds over the upper zone and diminished vesicular sounds with crepitations at the base. No other abnormal physical signs were found.

RADIOGRAPHS. There was considerable speculation at the time about the interpretation of the films but no definite conclusion was reached. Review of the films now, however, shows that their appearance would be consistent with a fluid-containing cyst in communication with a bronchus. The right hemithorax is totally opaque and contains an air-fluid level which, in the lateral view, is seen to be situated posteriorly (Fig. 1). In addition, hemivertebrae are present in the upper dorsal spine.

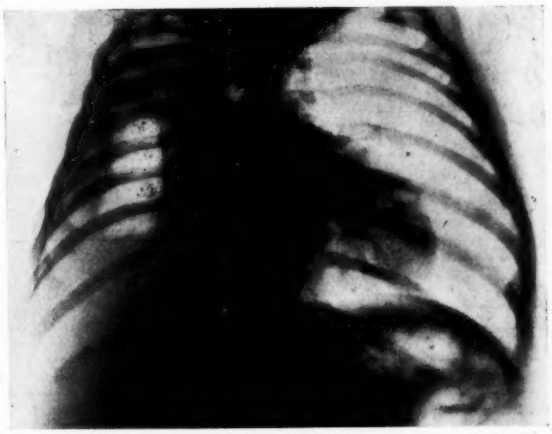

FIG. 1.—Radiograph showing air-fluid level in cyst in right hemithorax.

BRONCHOSCOPY. Bronchoscopy was performed on May 26, 1949. Vision was obscured by much mucoid secretion, but no obstruction was seen in the right bronchial tree.

BLOOD COUNTS. The following results were obtained: On 21.5.49, Hb 51%; 24.5.49, Hb 73%; 30.5.49, Hb 55%; 31.5.49, Hb 63% and leucocytes 15,000 (polymorphs 61%); 21.6.49, Hb. 50%.

TREATMENT. Blood transfusions were given by slow injection on May 23, May 30 and June 10 in amounts of 80, 50 and 80 ml. respectively, and penicillin, 30,000 units three-hourly by mouth, from May 31 to June 23 and again from July 2 until death.

On two occasions in the first four days after admission bright red blood was discharged through the nose. A genuine haemoptysis was first observed on June 9 and recurred daily for the next week. There was then an interval of freedom until the fatal massive haemoptysis occurred on July 3. These haemoptyses were accompanied by much frothy, watery fluid. There was a severe paroxysmal cough throughout. For the first

TABLE 1

ANALYSIS OF CASES REPORTED IN THE LITERATURE

	Author	Age	Sex	Presenting Symptoms	Operation	Result
1	Mixter and Clifford (1929)	22 months	Male	Fever, cough, dyspnoea	Two-stage	Recovered
2	Mixter and Clifford (1929)	7 weeks	Male	Difficulty in feeding	Cyst not located at operation	Died
3	Entz and Orosz (1930)	11 months	Male	Malnutrition	Marsupialization	Died
4	Fischer (1929)	6 months	Female	Cough	None	Died
5	Poncher and Milles (1933)	2 years	Male	Attacks of abdominal pain and melaena	Thoracotomy	Died
6	Böss (1937)	3 years	Male	Haemoptysis	Two-stage	Died
7	Seydl (1938)	3 months	Female	Cough and haemoptysis	None	Died
8	Lowry and Moorman (1938)	4 months	Not stated	Dyspnoea	Thoracotomy	Died
9	Nicholls (1940)	8 years	Female	Chronic empyema	One-stage excision	Recovered
10	Ladd and Gross (1940) (Case 2)	11 months	Not stated	Difficulty in swallowing and dyspnoea	Attempted excision	Recovered
11	Ladd and Gross (1940) (Case 4)	7 months	Not stated	Difficulty in swallowing and dyspnoea	Excised	Died
12	Ward and Krahl (1942) (Case 2)	9 weeks	Male	Cough and haemoptysis	None	Died
13	Schwarz and Williams (1942) (Case 1)	4 months	Male	Cyanosis and dyspnoea	One-stage excision	Died
14	Wyllie and Pilcher (1943)	1 year	Female	Poor weight gain	One-stage excision	Recovered
15	Ladd and Scott (1944) (Case 3)	7 months	Female	Cough and fever	Several operations	Died
16	Ladd and Scott (1944) (Case 4)	3 weeks	Male	None: detected by routine radiograph	Marsupialization followed by three other operations	Recovered
17	Ladd and Scott (1944) (Case 5)	2 years	Male	Haemoptysis	Several operations	Recovered
18	Laipply (1945)	1 day	Male	None	None	Died
19	Steele and Schmitz (1945)	15 years	Female	None: detected by routine radiograph	One-stage excision	Recovered
20	Valle and White (1946)	22 months	Female	Cough, cyanosis, haemoptysis	Thoracotomy	Died
21	Christoffersen (1947)	22 months	Male	None: detected by routine radiograph	One-stage excision	Recovered
22	Davidson and Brown (1947)	5 years	Female	Failure to gain	One-stage excision	Recovered
23	Davis and Salkin (1947)	14 years	Female	Pain in right chest	One-stage excision	Recovered
24	Jones (1947) (Case 1)	2 months	Male	Failure to gain	None	Died
25	Jones (1947) (Case 2)	19 months	Male	None: detected by routine radiograph	One-stage excision	Recovered
26	Ehler and Atwell (1948)	15 months	Male	Cough and haematemesis	One-stage excision	Recovered
27	Bickford (1949)	3 years	Male	Attacks of cough and dyspnoea	One-stage excision	Recovered
28	Doub (1951)	20 years	Female	None: detected by routine radiograph	One-stage excision	Recovered
29	Oterdoom (1951)	14 years	Female	None: detected by routine radiograph	One-stage excision	Recovered
30	Van Aken (1951) (Case 1)	3 years	Male	Cough and haemoptysis	One-stage excision	Recovered
31	Van Aken (1951) (Case 2)	1 year	Male	Cough and pneumonia	One-stage excision	Recovered

three weeks there was an irregular pyrexia to 102° F.; the temperature was normal for the next two weeks but fever recurred in the last week.

The infant gained slowly and with fluctuations, the last weight recorded being 8½ lb. on June 30.

NECROPSY. This was performed on July 4, 1949.

Abnormal findings were confined to the right lung. A cyst 1½ in. in diameter was attached to the dorsal segment of the right lower lobe (Fig. 2). This cyst, which was adherent on its posterior aspect to the parietal pleura, presented a lining of mucosa resembling that of the stomach and communicated with a cavity in the adjacent lung through a narrow channel also lined with mucosa. Immediately surrounding the opening of the communicating channel the pulmonary cavity was lined with mucosa but elsewhere the lining was of granulation tissue, except for a portion near a communicating bronchus lined with epithelium. The surrounding lung was collapsed and showed acute purulent infection. Blood clot filled the cavity in the lung; there was a small amount in the cyst.

Microscopically the cyst wall (Fig. 3) was composed of two layers of smooth muscle, muscularis mucosae and gastric mucosa. Continuity of the epithelial and muscular layers was demonstrable along the communicating channel up to a point just beyond the entrance into the cavity in the lung. Haemorrhage had arisen from the wall of this cavity in an area which gave the appearance of a peptic ulcer. Near the communicating bronchus the epithelium lining the cavity showed squamous metaplasia.

The pulmonary arteries showed considerable medial hypertrophy.

Case 2. M.N. was aged 3 months on admission to the Leicester Chest Unit on July 18, 1952.

He is the first child of healthy parents, and was delivered at term by forceps, weighing 6 lb. He was well until 7 weeks old, when he developed bronchitis: the cough persisted and at 10 weeks he had a haemoptysis. After this he became febrile and very dyspnoeic and refused feeds. He was therefore admitted two days later on July 4, 1952, to another hospital. Under treatment the respiratory distress subsided but his general condition did not improve and he had further haemoptyses. He was transferred to the Leicester Chest Unit on July 18, 1952.

FIG. 2.—Photograph of right lung with cyst attached showing lining of gastric mucosa. The glass rod is in the channel connecting the two portions of the cyst.

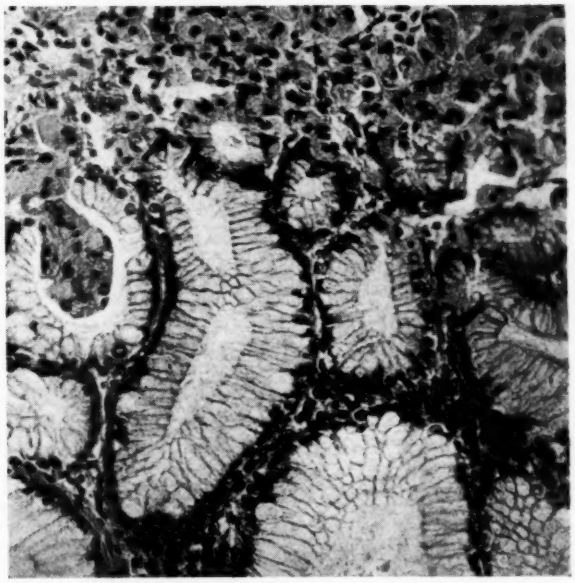

FIG. 3.—Photomicrograph of wall of cyst (haematoxylin and eosin ×190) showing gastric mucosa.

On examination his temperature was 100° F., the pulse 170 and respiration 40. Weight was 10½ lb. He was a pale, cyanosed, dyspnoeic infant. He had an external angular dermoid cyst over the right eye. The percussion note was impaired over the whole of the left side with diminished vesicular breath sounds accompanied by many crepitations. During examination he coughed up blood. This sputum gave an acid reaction with litmus paper. No other abnormality was detected.

A radiograph on admission showed that the whole of the left hemithorax was opaque. Hemivertebrae of the third to the seventh dorsal segments were also seen. On admission the red blood cells were 3,600,000, Hb 68% and leucocytes 18,700 (54% polymorphs).

In view of the haemoptysis and history of persistent pulmonary infection a diagnosis of a gastric cyst of the mediastinum was made and immediate operation decided on after an intravenous blood drip had been set up.

FIRST OPERATION. G.C. operated on July 18 with the infant in the lateral position. The chest was opened through the bed of the resected sixth left rib. The lung was extensively adherent. A cystic structure was found lying in the interlobar fissure. The lining of the cyst appeared to be of mucous membrane. In its base, and communicating with the lung, was a punched-out hole having the appearance of a peptic ulcer. The cyst was removed by sharp dissection. Further inspection of the pleural cavity revealed a second cyst lying in the paravertebral gutter at the level of the sixth rib but, owing

to the baby's poor general condition, it was considered prudent to leave this cyst, as it appeared to be uncomplicated, for removal at a subsequent operation. The chest was then closed.

On the day after operation the baby's general condition was much improved. Haemoglobin was 90%. A radiograph of the chest on July 22 showed considerable clearing of the left lung field. He began to gain weight, and penicillin, which had been given since admission, was stopped on July 29. On August 2, however, he began to lose weight and again became dyspnoeic. The percussion note at the left apex again became impaired and penicillin was restarted. On August 6 he had a haemoptysis and next day a lateral radiograph of the chest showed a small fluid level situated posteriorly in the left chest in the position of the cyst noticed at operation. It was therefore thought advisable to remove this cyst.

FIG. 4.—The second cyst removed at operation opened out to show the lining gastric mucosa.

SECOND OPERATION. The previous incision was re-opened on August 7 by G.C. The cyst was encountered lying deeply buried behind the aorta and oesophagus. It was removed by scissors dissection.

Progress following this operation was uninterruptedly good. The baby gained weight and had no further haemoptyses. A chest radiograph on August 12 showed almost complete aeration of the left lung. When he was discharged on August 27 at the age of 4½ months he weighed 12 lb. 13 oz. Haemoglobin was 99%.

PATHOLOGICAL REPORTS. Dr. D. B. Cruickshank reported as follows:

Specimen from First Operation. 'Microscopically the cyst wall is mainly composed of unhealthy granulation tissue with a zone of older fibrosis beneath this and beyond inflamed lung. In places in the cyst wall can be seen open crypts lined with cuboidal epithelium with more deeply placed transversely cut glandular acini. There are also some isolated strands of polygonal cells suggestive of secretory epithelium. The picture is consistent with that of an inflamed necrosing gastric mucosa but it is impossible to affirm that the structure is in fact gastric mucosa.'

Later, comparing this section with that of the second cyst, Dr. Cruickshank reported that he considered that the two were of identical structure.

Specimen from Second Operation. 'Macroscopically the cyst (Fig. 4) measures 3×3×2·5 cm. and has a smooth exterior except for rough attachment areas. Its wall is 0·5 cm. thick, has an outer areolar, intermediate white "cartilaginous" and an inner thick ridged mucosal layer. The "cartilaginous" layer is 0·4 cm. thick over part of the wall.

Microscopically this is a classic gastric cyst (Fig. 5). The structure of the lining and wall has all the features of a fundal mucosa and musculature, except that the three plain muscle layers have undergone some type of hyalo-degeneration accounting for the "cartilage"-like appearance mentioned in the macroscopic description. There is no evidence of inflammation and all histological structures are very clearly defined.'

Discussion

A number of hypotheses have been advanced to explain the origin of intra-thoracic gastric cysts; the most generally accepted and, it seems to us, the most likely explanation is that they arise from a bud pinched off from the embryonic foregut (Mixter and Clifford, 1929). In the 4 mm. embryo the lungs and trachea are represented by a mass attached to the ventral surface of the oesophagus: the lower part of this mass constitutes the site of the division of the bronchi from the trachea whose cavity is still in free communication with the

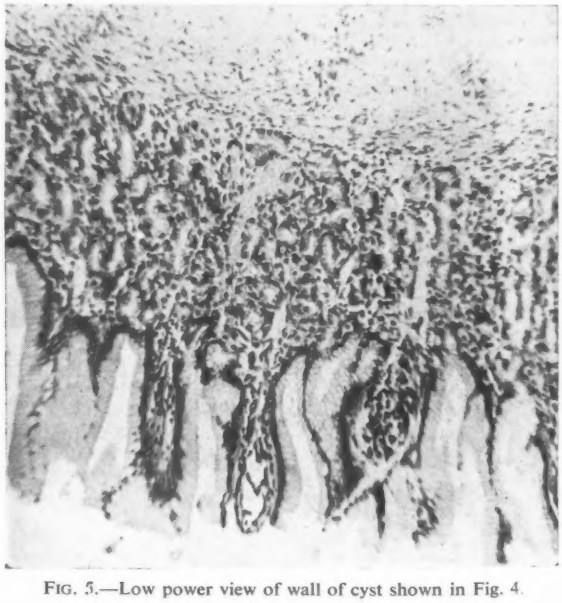

FIG. 5.—Low power view of wall of cyst shown in Fig. 4.

oesophagus. The trachea becomes separated from the oesophagus by the downward growth of the lung buds and the upward extension of the notch between the lung buds and oesophagus. At this stage an outbud of foregut containing entoderm and mesoderm and destined to become stomach could be pinched off. This hypothesis would also explain the almost invariable situation of these cysts on the right since the stomach normally rotates to the right during development.

Symptoms can be divided into three groups, those resulting from pressure, those from functional activity of the cyst and those from infection. Both our cases showed all three. In the first group are cough, dyspnoea, cyanosis, wheezing and occasionally pain; in the second haemoptysis; and in the third pyrexia and interference with nutrition. Pressure symptoms are usually continuous but may occur in attacks which, Olenik and Tandatnick (1946) suggest, are due to varying amounts of secretion in the cyst. Presenting symptoms are usually those of pressure and/or infection which frequently occurs (Jones, 1947). Haemoptysis as a presenting symptom is unusual but has been noted in other cases. It is difficult in young babies to distinguish haemoptysis from haematemesis, a difficulty encountered by us in Case 1 and noted also by other observers (Ladd and Scott, 1944). In 75% of the reported cases symptoms have started in the first year of life (Jones, 1947): seven cases (Table 1) have only been detected by routine radiographs, and Valle and White (1946) consider that in those cases in which symptoms do not occur early the cysts are functionally inactive. It seems probable that the fluid coughed up with the blood in Case 1 was gastric juice but no tests were made: in Case 2 the fluid was acid to litmus.

Neither physical signs nor the x-ray picture are characteristic and superadded infection may make identification of the cyst difficult. A cyst situated posteriorly and on the right may suggest a gastric cyst, since all those reported have been in this situation except for two on the left described by Jones (1947) and our Case 2: they are usually in the middle third of the thorax.

It is naturally impossible to make a correct preoperative diagnosis of a gastric cyst unless functional activity can be demonstrated. The occurrence of haemoptysis in a young infant is very suggestive since it is at this age a symptom rarely encountered. Tapping the cyst to demonstrate the activity of its contents as has been done (Jones, 1947); Mixter and Clifford, 1929; Ehler and Atwell, 1948) is not advisable, not only on account of the risks inherent in such an operation, but because gastric juice leaking along the needle track may cause digestion of surrounding structure as has been noted in the skin following marsupialization of the cyst (Thompson, 1947). The diagnosis of a bronchial angioma was considered in Case 1. Bronchoscopy was unhelpful because of the large amount of mucus present and thoracotomy was not considered advisable in view of the infant's poor general condition. The correct diagnosis, as in most of the other recorded cases, was not suspected but in retrospect this was a typical case. In Case 2, profiting by experience, the correct diagnosis was made on the strength of the haemoptysis, the acid sputum and persistent pulmonary infection. It is of interest that both cases showed hemivertebrae, an associated abnormality noted by other observers.

Most gastric cysts are unilocular and single; in Case 1 the cyst was bilocular and peptic ulceration occurred in only one of the portions, rupturing into the lung and causing the haemoptysis. Gastric cysts are usually about the size of those in the present cases but Poncher and Milles (1933) recorded one 12 cm. in diameter and Wyllie and Pilcher (1943) comment on the difficulty of distinguishing a large cyst from an effusion. Rarely, more than one cyst, as in Case 2, may be found (Poncher and Milles, 1933; Ward and Krahl, 1942).

In the past operative removal has been attended by a high mortality but in recent years, with improvement in thoracic surgery, more successful results have been obtained. Before 1940 operation was performed in six cases of which only one recovered. Since 1940 removal of the cyst has been carried out in 20 cases, in 16 of which a successful outcome has resulted: the youngest patient on whom operation has been performed successfully was 3 weeks old (Ladd and Scott, 1944). Most authorities agree that the operation of choice is removal in one stage, but Ladd and Scott (1944) and Ladd and Gross (1940) advise marsupialization first followed by removal later. There is, however, a danger of excoriation of the skin with this method. Ladd and Scott (1944) stress the intimate attachment of these cysts to the oesophagus and state that they may share a common muscular wall, but the experience of other observers seems to indicate that this is unusual.

We wish to thank Dr. J. Vernon Braithwaite for permission to report Case 1, Dr. G. H. Valentine for referring Case 2, Dr. J. N. Dearnally for the post-mortem report of Case 1, Dr. D. B. Cruickshank for the pathological reports on and photomicrograph of Case 2, Miss C. van Dorp, F.R.C.S., for some of the translations, and Mr. E. V. Willmott for the photomicrograph of Case 1.

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TOTAL DRAINAGE OF PULMONARY VEINS INTO THE RIGHT ATRIUM

BY

S. T. WINTER, E. N. EHRENFELD and J. FELDMAN
From the Hadassah University Hospital, Jerusalem, Israel

(RECEIVED FOR PUBLICATION JUNE 13, 1952)

Anomalies of the pulmonary venous return are uncommon, particularly malformations with total drainage of the pulmonary veins directly into the right atrium. Brody (1942) reviewed the literature on anomalous pulmonary venous drainage, dealing with 106 cases, including four personal ones. Further necropsy reports have since been presented by Vass and Mack (1949) and Smith (1951), the latter also noting details of additional cases in the literature. Recent case reports by Johnson and McRae (1948), Dotter, Hardisty and Steinberg (1949), Knutson, Taylor, Pruitt and Dry (1950), Friedlich, Bing and Blount (1950), Grishman, Brahms, Gordon and King (1951), and Muller (1951) have dealt with patients diagnosed during life by means of angiocardiography and cardiac catheterization. Out of a total of 182 cases of anomalous pulmonary veins thus reported in the literature, 30 showed total anomalous drainage of the pulmonary veins into the right atrium or the coronary sinus.

The embryology of total pulmonary drainage into the right side of the heart has been discussed by Brody (1942) and by Brantigan (1947). Taussig (1947) has described fully its clinical aspects. The systemic circulation can only receive oxygenated blood from the right side of the heart via a patent foramen ovale. As the right side of the heart receives blood from both the systemic and pulmonary circulations, pulmonary congestion usually results from the excessive pulmonary blood flow. As suggested by Brody, decompensation in these cases presumably occurs with the gradual narrowing of the foramen ovale and the obliteration of the lumen of the ductus arteriosus, thus precipitating cardiac failure. The electrocardiogram is helpful, for there are few other congenital heart lesions without cyanosis and frequently without a murmur, showing right axis deviation on the electrocardiogram.

Partial anomalous venous drainage of the pulmonary veins is encountered occasionally in adults without symptoms, whereas total anomalous venous drainage is usually fatal in the first six months of life. Interest in this malformation, however, is increasing because of the possibilities of diagnosis during life and of surgical treatment. Muller (1951) has reported a successful operation on a 4-year-old girl with complete transposition of the pulmonary veins. Anastomosis between the left auricular appendage and pulmonary vein resulted in the disappearance of cyanosis and the ability to assume normal activities. Muller also performed a similar operation on an adult woman, but she died shortly afterwards. It is probable that earlier diagnosis by cardiac catheterization and angiocardiography will be needed for reparative surgery to be successful. Cardiac catheterization will show an oxygen content of the blood in the right auricle higher than that in the superior vena cava, and also the catheter may enter the pulmonary vein directly from the right auricle. The oxygen concentration of the blood in the femoral artery will be equal to that in the right side of the heart where there is total anomalous drainage, but will be higher if the anomalous drainage is only partial.

The following case, in which all four pulmonary veins entered the right atrium directly, presented the usual features of this malformation.

Report of a Case

A girl of Oriental Jewish parentage was admitted at the age of 10 weeks because of breathlessness.

The infant was born at full term after an uneventful pregnancy, appearing normal at birth, and weighing 2,100 g. She was breast fed, and had been ill on several occasions with short bouts of fever and vomiting. The mother noticed that the child frequently had difficulty in breathing and sometimes even became blue. About 16 hours before admission the infant began to cough slightly and did not eat or sleep as usual. Four hours before admission she became distressed and cried

repeatedly, cyanosis and shortness of breath becoming marked.

On examination she appeared to be a fairly well nourished infant, acutely ill, restless, cyanotic, crying out in distress and gasping for breath. The temperature was 37° C., pulse rate 120 per minute, weight 3,900 g. Breathing was rapid and shallow, mainly abdominal, with working of the alae nasi, tugging of the neck muscles and retraction of the lower ribs. The apex beat was heard in the fourth intercostal space 1 cm. lateral to the left mid-clavicular line. Percussion showed the heart to be enlarged in all directions; the heart sounds were clear and the heart action rhythmic. On percussion there was some impairment of resonance at the right lung base posteriorly, with corresponding reduced air entry but without adventitious sounds. The liver edge was smooth and palpable about 3 cm. below the right costal margin, and the spleen tip was felt under the left costal margin. The fingers were not clubbed.

A blood count gave: red cells, 4·3 m. per c.mm., haemoglobin, 10·5 g.%, white cells, 11,400 per c.mm. The Mantoux reaction (1 : 1,000) was negative. A radiograph of the chest on admission showed an enlarged heart with clear lung fields.

The infant was given oxygen with a resultant slight improvement in respiration. On the following day she was apathetic and very restless. Cyanosis had increased, and breath sounds at both lung bases were further decreased. A faint systolic murmur was heard internal to the apex beat. The liver edge appeared to be 1 cm. lower than on the previous day. A second radiograph (Fig. 1) showed an enlarged globular heart with poor

FIG. 1.—Chest radiograph.

pulsation, and reduced translucency of the right lung base and left mid-zone. On the third day in hospital she was much weaker, breathing in gasps. Dullness at the right base was more marked, and breath sounds were further reduced at both bases, especially at the right. Fluoroscopy was repeated and showed very slight heart pulsations, with a normal oesophageal outline on a barium swallow. Four hours later an E.C.G. was recorded, and the child died during this procedure.

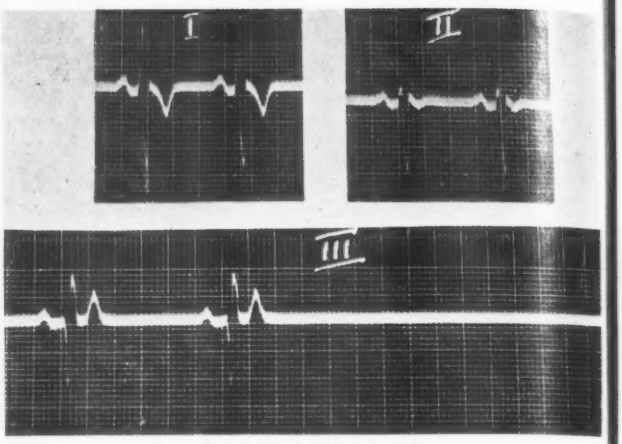

FIG. 2.—Electrocardiogram.

ELECTROCARDIOGRAM REPORT. There were large bidirectional ventricular initial complexes with deep negative T waves in lead I, large Q waves and peaked positive T waves in lead III (Fig. 2). There was extreme shortening of the Q-T interval before final asystole recorded in lead III.

NECROPSY REPORT. The principal abnormal findings were confined to the heart and lungs. All other organs were not unusual. The heart weighed 65 g. The right atrium was markedly enlarged, and its lumen included that of the distended right auricular appendage. Its wall measured up to 3 mm. in thickness. The right ventricle was enlarged with hypertrophy of its wall, and the tricuspid valve was not unusual. The left atrium was rudimentary, measuring about 1·5 cm. in diameter. There was no entry of the pulmonary veins into the left atrium. Instead, all four pulmonary veins entered the posterior wall of the right atrium (Fig. 3). The right ventricle was approximately three times the size of the left ventricle, which was about normal in size for a baby of this weight and age. The papillary muscles were flattened or non-existent over most of the inner surface. The mitral valve was small, measuring 2 cm. in circumference. The only communication between the right and left sides of the heart was through a patent foramen ovale with a lumen of approximately 2 × 5 mm. The pulmonary artery was enlarged, being larger than the aorta. The ductus arteriosus was still patent with a lumen of about 1 mm. in diameter. The coronary arteries were not remarkable, originating in the usual anatomical position and taking a normal course. Several small haemorrhages were noted over the heart surface, particularly anteriorly.

Both lungs were covered with a thin transparent membrane, and were mottled externally red and blue. The blue regions were depressed and quite extensive. On section the same mottling was found. The cut surface was moist, spongy or haemorrhagic. The pulmonary vessels appeared enlarged, particularly the main branches.

Microscopic examination showed no significant changes in the body organs, with the exception of the

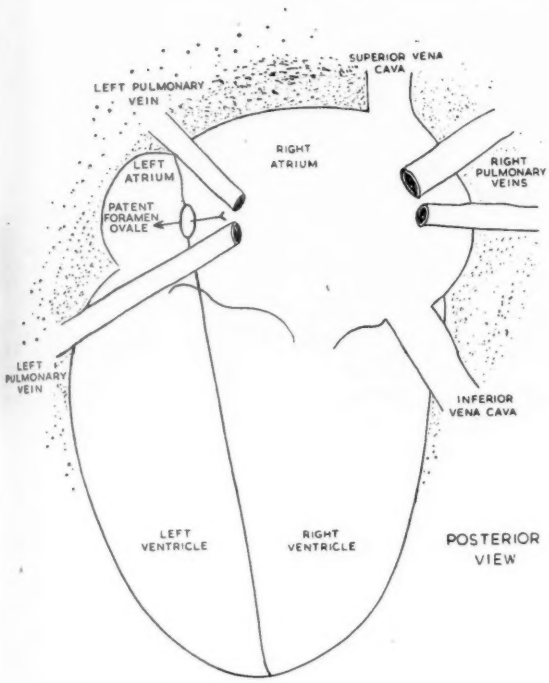

FIG. 3.—Scheme of posterior aspect of heart drawn at necropsy.

liver, where congestion with fatty change was noted.

The pathological diagnosis was congenital heart disease; transposition of all pulmonary veins to the right atrium; a patent foramen ovale and a rudimentary left atrium; hypertrophy and enlargement of the right ventricle and right atrium; patent ductus arteriosus; pulmonary atelectasis.

Summary

A case of drainage of all pulmonary veins into the posterior wall of the right atrium is reported.

We wish to thank Professor B. Gruenfelder for permission to publish this report, and Dr. S. Berman and Dr. S. Shorr for their help.

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THE INCIDENCE AND NATURE OF INTRACRANIAL CALCIFICATIONS AFTER TUBERCULOUS MENINGITIS

BY

JOHN LORBER

From the Department of Child Health, University of Sheffield

(RECEIVED FOR PUBLICATION MAY 13, 1952)

Intracranial calcifications following tuberculosis of the central nervous system have until recently been rare. This is surprising considering the high incidence of intracranial tuberculomata and the frequency with which tuberculous lesions calcify in other parts of the body.

During the second half of the nineteenth century tuberculomata were considered to account for approximately half of all intracranial 'tumours' (White, 1886; Starr, 1890). Since then there has been a progressive diminution of both their absolute and relative incidence, but even in 1925 Critchley found that tuberculoma was the commonest intercranial tumour in his selected series of 125 children (no figures given). In a study of necropsy material collected in Leeds between 1910 and 1931 Garland and Armitage (1933) found that of 264 intracranial tumours 33·8% were tuberculomata. Other reports (van Wagenen, 1927; Walshe, 1931; Cushing, 1932; Stern, 1937; Zülch, 1938; Dott and Levin, 1939; Wilson, 1940), chiefly from neurological centres, put their incidence very much lower. In 1949 Walker and Hopple thought that less than 1% of all intracranial tumours in the U.S.A. were tuberculomata. In countries where tuberculosis is still very prevalent the proportion of tuberculomata among intracranial tumours is still high (Asenjo, Valladares and Fierro, 1951).

From the available data it is impossible to calculate the incidence of calcification of intracranial tuberculomata. In a partial review of the literature Scott and Graves (1933) found 11 instances among 815 cases, representing 1·35%. The rarity of calcifications may partly be due to the poor prognosis in cerebral tuberculoma and partly to absence of radiological studies.

In an extensive search of the literature of the past 100 years I was able to find 49 examples of intracranial calcifications where these were proved or believed to have been calcified tuberculomata. Thirteen of these were discovered at necropsy (Table 1) and 36 were found on x-ray examination of the skull (Table 2). Fourteen of the latter were subsequently verified at operation or necropsy, but in the 22 others the tuberculous nature of the lesions remained conjectural. Even histological examination was not decisive in old-standing cases, as the lesions had lost the specific features of tuberculoma.

Most patients with calcified tuberculomata suffered from gross neurological lesions, had epilepsy, and many were mentally retarded. The tuberculomata were situated either in the hemispheres or in the cerebellum, but taking the small size of the cerebellum into account, tuberculomata seemed to have a predilection for this site. The calcified lesions were single or multiple, and Weens (1948) reported as many as 11 foci in one patient.

Radiologically the calcified tuberculomata are stated to have a characteristic, serrated and angular appearance (Weens, 1948; Weinberger and Grant, 1942), varying from 0·5 to several centimetres in diameter. The centre of the shadow is often less dense, because of its caseous nature. The calcification begins in the periphery of the lesions, and, as the central portion shrinks and undergoes resorption, the calcareous shell fragments, giving its characteristic appearance. Eventual ossification of the lesions is stated to be not uncommon (Camp, 1930 and 1948). Most of the previously described calcified lesions were discovered in their fully developed stage. Cushing (1932), however, observed two patients with intracranial tumours which were proved to be tuberculomata at operation and were left *in situ*. The patients recovered and eventually calcification could be demonstrated in radiographs of the skull.

Small intracranial tuberculomata may remain silent until tuberculous meningitis supervenes. As tuberculous meningitis was almost uniformly fatal until the advent of streptomycin, it is not surprising that apart from the remarkable cases of Foà (1903)

TABLE 1
CALCIFIED TUBERCULOMATA DISCOVERED AT NECROPSY

No.	Author	Age and Sex	Clinical Features	Pathological Findings
1	Ogle (1864)	36 F	Cerebral symptoms for 1 month	Calcified tuberculoma in velum interpositum; enlarged ventricles; meningitis
2	Ogle (1864)	child	Convulsions	Calcified tuberculoma, size of hazelnut, in right cerebellum
3	Lancereaux and Lackerbauer (1871)	65 M	Right hemiparesis for 61 years	Calcified tuberculoma, size of hazelnut, in left thalamus
4	Dunlop (1893)	8 F	Headache, ataxia, right hemiparesis and blindness for 14 months. Died of tuberculosis meningitis.	Bean-sized calcified tuberculoma in right cerebellum
5	Siemon (1893)*	? ?	?	Solitary calcified and ossified tuberculoma, 4·5×2·5 cm., in frontal lobe
6	Foà (1903)	10 M	Recovered from 'meningitis' in infancy; died of nephritis	Hydrocephalus; calcified tuberculoma in left cerebellum
7	Stewart (1927)	23 M	Headaches; extensive tuberculosis; died of Addison's disease	Dense, hazelnut size calcified tuberculoma in right lobe of cerebellum
8	Smith (1927)	62 F	Left hemiparesis for 58 years	Stony, hard, calcified tuberculoma in right cerebral hemisphere and lenticular nucleus
9	Garland and Armitage (1933)†	50 M	—	Patchily calcified tuberculoma in left frontal lobe
10	Evans and Courville (1938)	10½ M	Recovered from 'tuberculous meningitis' at 3 years of age; T.B. of bone; died of generalized convulsions	Calcified tuberculoma, 3×1·3×0·7 cm., in right frontal lobe; hydrocephalus; non-calcified tuberculoma in left cerebellar hemisphere
11	Evans and Courville (1938)	6 M	Listlessness and irritability for three weeks; tuberculous meningitis	Several calcified and ossified tuberculomata in both cerebral hemispheres
12	Robles (1943)‡	? ?	—	No details available
13	Lopez Clares (1944)‡	? ?	—	Calcified tuberculoma in right parietal lobe

* Reported by Ström. † Also re-described Stewart's case (No. 7). ‡ Original articles not available.

and of Evans and Courville (1938) no instances following possible tuberculous meningitis have been reported. Foà's patient, a boy of 10 years of age, was stated to have recovered from 'meningitis' in infancy, but with residual hydrocephalus. He died of nephritis. At necropsy a calcified tuberculoma was found in the cerebellum. One of Evans and Courville's patients (Case 2) appears to have suffered from 'serous tuberculous meningitis' at 3 years of age. He died seven years later of extensive tuberculosis. At necropsy there was a calcified tuberculoma in the right frontal lobe and a fresh tuberculoma in the cerebellum. Basal adhesions and hydrocephalus were evidence of an old meningitic process. Apart from a patient of my own (Lorber, 1951b) and one of Koch (1951) no intracranial calcification has yet been reported in cases of tuberculous meningitis treated with streptomycin. Indeed, calcification following any form of meningitis was stated to be of great rarity (Camp, 1948) unless the meningitis was associated with encephalitis. Levinson and Hartenstein (1951) reported massive intracranial calcification seven months after severe pneumococcal meningitis in an infant who remained deaf, blind, epileptic, severely retarded, and had generalized rigidity. Camp (1948) found intracranial calcification in two children after polioencephalitis.

Present Investigation

The present investigation started because it appeared that there might be an appreciable incidence of intracranial calcification in patients who recovered from tuberculous meningitis. For this reason radiographs of the skull were taken on admission of each child admitted with tuberculous meningitis, and at approximately three to six month intervals in all survivors. No calcifications were found either on admission or during the course of treatment.

The material of this investigation consists of all the first 25 surviving children treated at the Children's Hospital, Sheffield, who survived from a minimum of two and a half years to a maximum of four and a half years after the onset of tuberculous meningitis. All the children are well and free from any evidence of active infection, although some have certain neurological sequelae. In addition, reference will be made to two children who died 21 and 29

TABLE 2

PROVED AND UNPROVED CALCIFIED INTRACRANIAL TUBERCULOMATA DISCOVERED DURING LIFE

No.	Author	Age and Sex	Clinical Features	X-ray Findings	Operation or Necropsy Proof	Comment
1	Klieneberger (1909-10)	12 M	Positive tuberculin; increasing headaches, vomiting, papilloedema, blindness, drowsiness, spasticity	Mass in region of corpora quadrigemina made up of 3 individual lesions	—	May have been a tumour
2	Sabat (1913)	17 ?	Left-sided convulsions for 3 years followed by permanent hemiplegia and blindness	Walnut-sized calcified mass in right hemisphere	Removal at operation, died of tuberculous meningitis few days later	—
3	Ström (1919-21)	21 F	Convulsions of increasing frequency for 12 years; right-sided hemiparesis	Calcified mass, 3·5×3 cm., in left frontal lobe	Removed at operation; died next day. Histology, calcified and partly ossified mass	No specific tissue detected on histological examination
4	Kingreen (1924)	10 M	—	Two calcified shadows in hemispheres	One removed at operation; died 4 days later. Second lesion at necropsy had tuberculous granulation tissue	—
5	Sauer (1928)	7 M	Convulsions for 5 years; hemiplegia (right); tuberculin positive	Five calcified shadows, all on left side	—	—
6 and 7	Cushing (1927) and Cushing (1932)	14 M ? ?	Signs of increased intracranial pressure thought to be due to cerebral tumour	Progressive intracranial calcification	Exploratory operation; tuberculoma found and left *in situ*	See text
8	Paterson and Stevenson (1930)	16 M	Convulsions	Solitary calcified mass in right parietal lobe	Removal at operation; central caseous mass	Survived
9	Puusepp and Zlaff (1933)	24 F	Ataxia and blindness for 3½ years	Calcified mass right occipital area	Removed at operation. 'Proved tuberculoma'	
10	Puusepp and Zlaff (1933)	18 F	Ataxia and later quadriplegia for 10 years	Midline calcified mass in region of hypothalamus	Proved at necropsy	
11	Puusepp and Zlaff (1933)	29 F	Headaches, convulsions, blindness for 8 years	Calcified shadow size of hen's egg in right temporal lobe	—	
12	Vincent *et al.* (1933)	7 M	Convulsions from 15/12 of age	Calcified shadow, size of hazelnut in right parieto-occipital region	Removed 1 year later, histological proof; alive 23/12 after operation	
13	Borchardt (1933)	6 M	Cerebral symptoms for 4¾ years; admitted with meningitis and died	Four calcified shadows	Histological proof at necropsy	See text
14	Coenen (1937)	19 M	Bony tuberculosis in childhood; convulsions for years	Calcified shadow in right occipital lobe	Calcified amorphous mass, 5·5×4·5×4·0 cm., removed at operation	
15-21	Martin (1937)	Adults	All patients had convulsions and past history or present evidence of tuberculosis elsewhere in body	One to several dense calcified shadows, almost all above the tentorium	One lesion removed in Case 3 and found to be amorphous calcified mass	

months after the onset of meningitis. The treatment of these children was described elsewhere (Illingworth and Lorber, 1951).

Intracranial calcifications were radiologically demonstrated in 17 of the 25 surviving children. The length of observation from the beginning of the treatment of meningitis is shown in Table 3. In many children it was possible to observe the evolution of these calcifications, but sometimes early traces of calcifications were only detected in retrospect. In other cases shadows suggestive of early calcifications did not develop into significant lesions.

No calcifications were detected in any patient in less than 18 months from the beginning of treatment (Table 4). In 13 of the 17 the calcifications were discovered between two and three years after the onset of meningitis. In the eight negative cases the latest radiograph of the skull was taken between 29 and 50 months from the beginning of treatment and in five of these after the thirty-ninth month.

The lesions are divided into three different types according to the situation and appearance of the calcified shadows. More than one type of lesion was seen in three children, including two in whom

TABLE 2—*continued.*

No.	Author	Age and Sex	Clinical Features	X-ray Findings	Operation or Necropsy Proof	Comment
22	Evans and Courville (1938)	8 M	Increasing headaches for 5 years, aphasia, left hemiplegia	Calcified mass, 6×7·5 cm., in right parieto-occipital region	Histological proof at necropsy	
23	Bailey (1938)	7 M	Convulsions, tuberculin-positive, primary abdominal tuberculosis	Calcified shadow left posterior parietal region	—	
24	Pancoast *et al.* (1940)	28 M	Attacks of dizziness from age 7 to 21 years, followed by headaches	Large solitary calcified mass to the left and in front of pineal	Could not be found at operation	
25	Pancoast *et al.* (1940)	15 M	Pulmonary tuberculosis; no details given	Several calcified shadows	—	
26	Camerer (1940)	10 F	Primary tuberculosis	Bean-sized calcified lesion behind and above the sella	Proved at necropsy	
27	Camerer (1940)	10 M	Primary tuberculosis of lung at 3½, papilloedema, headache; normal C.S.F.; quadriplegia; negative skull radiograph; remained an idiot	Incipient calcification in posterior fossa at 4½. At 10 years, large plum-sized mass in posterior fossa	—	
28	Weinberger and Grant (1942)	12 M	Convulsions and left hemiplegia; healed primary pulmonary T.B.	Calcified shadow right parieto-occipital region	Removed at age of 15; histological proof	
29, 30	Penfield and Ward (1948)	? ?	Epilepsy; no details given	?	—	Very doubtful; no evidence given
31	Weens (1948)	1½ F	Accidental discovery in tuberculous infant without cerebral symptoms who died of T.B.M. at 3	Several calcified shadows in all areas	Eleven calcified tuberculomata found, some with active caseation	See text
32	Weens (1948)	1½ M	Primary tuberculosis of lung; tuberculosis of rib and mandible	Four calcified shadows	Died ? cause; no necropsy	
33	Weens (1948)	9 M	Known T.B. from age of 1 year; convulsions at 3 and 5; healthy later; accidental discovery after head injury	Serrated, oval calcified shadow, 7×10 mm., in right parieto-occipital region	—	
34, 35	De Sa (1949)	? ?	No data given	Calcification in two cases	One 'confirmed' at operation	Doubtful cases; no evidence given
36	Koch (1951)	3 M	Tuberculous meningitis treated with streptomycin; residual left hemiplegia 14/12 after onset	Extensive calcifications in right parietal region found at encephalography	—	See text

calcification of the falx cerebri was detected. As calcification of the falx is common under physiological conditions in adults over 30 years of age (Camp, 1930), it may not necessarily be pathological in children. For this reason these calcifications will not be further considered.

In eight children calcified lesions were seen which were situated apparently within the brain substance (Figs. 1 and 2). In seven of the eight a solitary intracerebral calcified shadow was found, but in a previously reported case two shadows were

TABLE 3

INTRACRANIAL CALCIFICATIONS IN RELATION TO THE LENGTH OF OBSERVATION*

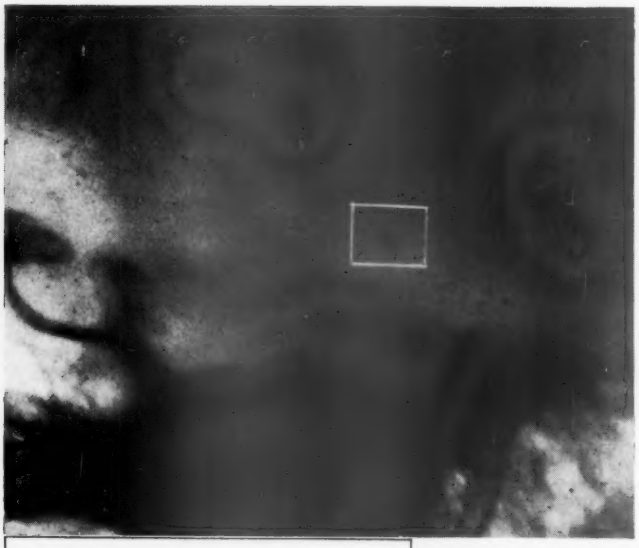
Length of Observation (years)	Total Number of Cases	Number with Calcifications
4 —4½	6	4
3½—4	5	4
3 —3½	5	3
2½—3	9	6
2½—4½	25	17

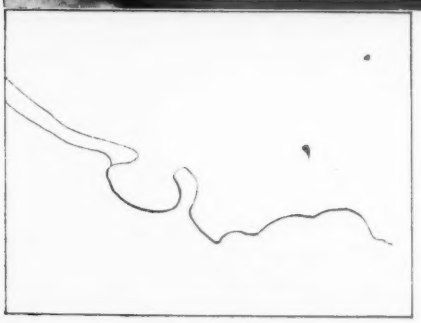
* Survivors only.

TABLE 4

FIRST APPEARANCE OF CALCIFICATION FROM BEGINNING OF TREATMENT IN 17 PATIENTS

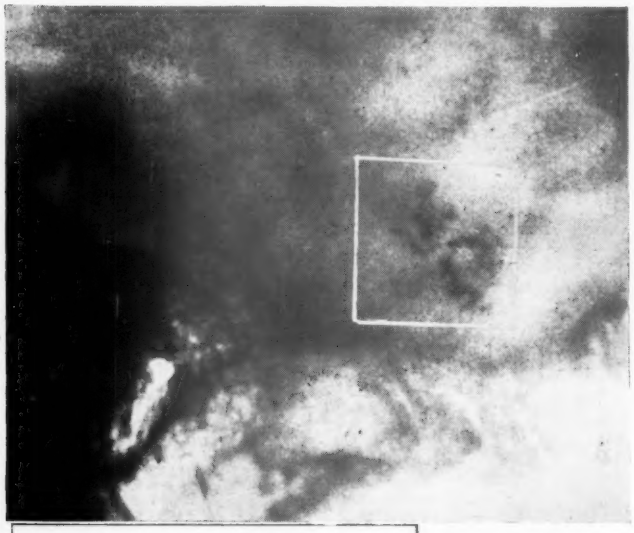
Period	Number
Up to 18 months	0
19—24 ,,	3
25—30 ,,	6
31—36 ,,	7
37—42 ,,	1
Over 42 ,,	0



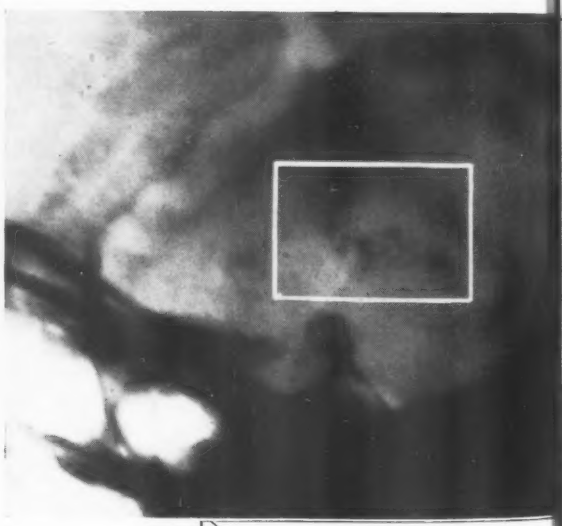


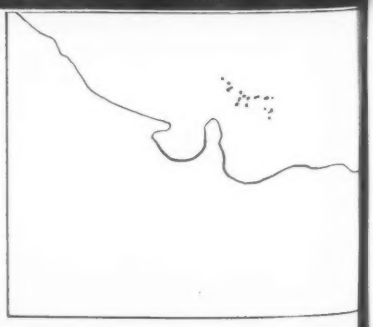
FIGS. 1 and 1a.—Small calcified shadow, ? in the parietal lobe of the brain first seen 29 months after onset of meningitis; grew in size and density during next 15 months (Case 10).

FIGS. 3 and 3a.—Basal calcification above and behind sella first noticed 31 months after onset of meningitis. It increased in size subsequently (Case 12).

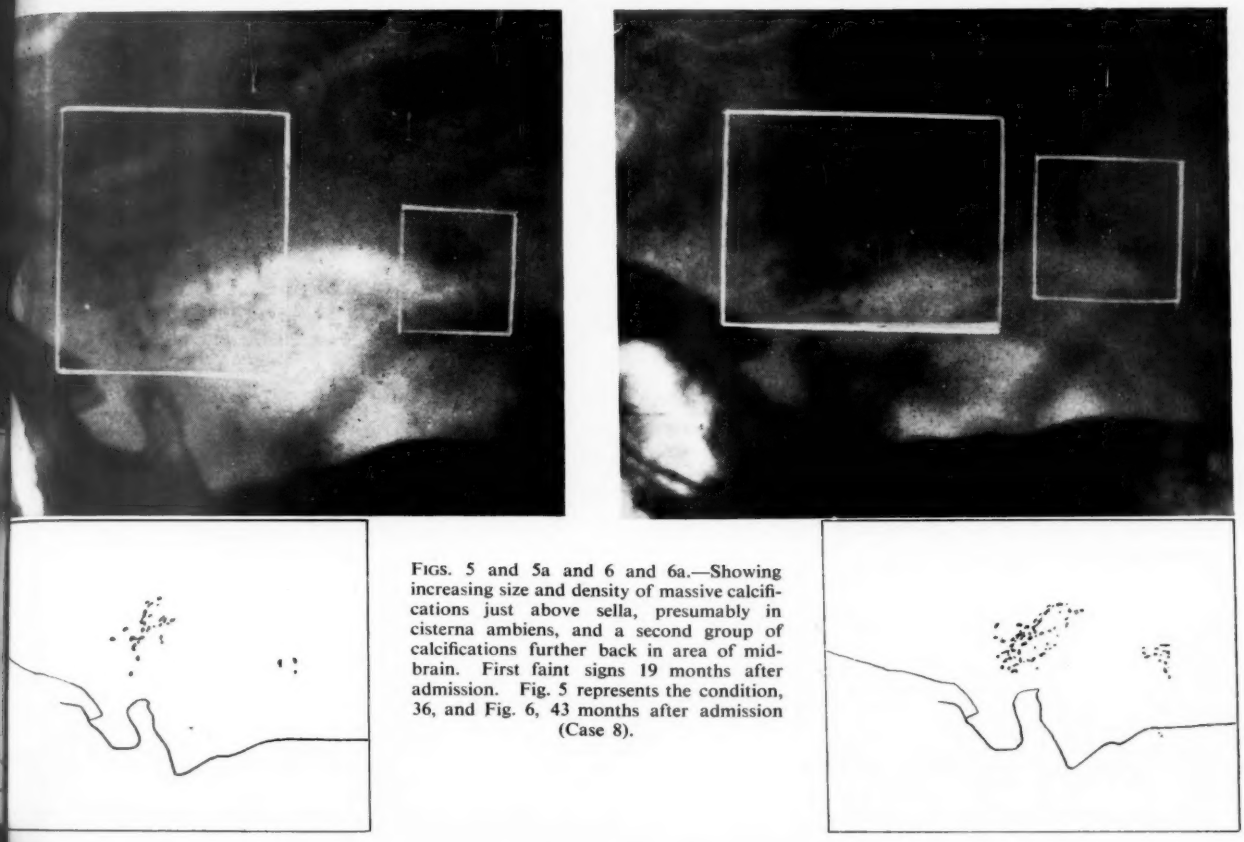


FIGS. 2 and 2a.—Cluster of intracerebral calcifications apparently in occipital lobe. First seen 36 months after onset of meningitis; became denser in next 12 months (Case 6).





FIGS. 4 and 4a.—Plaque-like basal calcification above sella faintly seen 36 months after onset of meningitis; much denser and longer in next 12 months (Case 5).



FIGS. 5 and 5a and 6 and 6a.—Showing increasing size and density of massive calcifications just above sella, presumably in cisterna ambiens, and a second group of calcifications further back in area of midbrain. First faint signs 19 months after admission. Fig. 5 represents the condition, 36, and Fig. 6, 43 months after admission (Case 8).

present (Lorber, 1951b). Most of these calcifications were small, with a diameter of a few millimetres (Fig. 1). The bigger shadows in the present series were composed of clusters of numerous small calcified foci (Fig. 2).

In 11 children more spectacular and less expected calcified shadows were found at the base of the brain.

These calcifications were either immediately above or above and behind the sella (Figs. 3-6). Most were of plaque-like appearance, straight, curved or branching shadows (Figs. 3-4). These, too, were composed of clusters of smaller, individual shadows. In other cases much bigger, conglomerate masses of calcifications were seen (Figs. 5 and 6). They were easily demonstrable on lateral radiographs of the skull, but because of their position at the base they were hidden by the paranasal sinuses and other structures of the face on the antero-posterior view. Towne views and stereoscopic lateral radiographs showed that these calcifications were either in or very near to the midline, in the approximate situation of the main basal subarachnoid cisterns. The site and incidence of these calcifications corresponded closely both with the site and the incidence of tentorial obstructions, which were demonstrated by encephalography. In encephalograms a large air bubble is seen to be held up just above the sella, in the cisterna ambiens and other basal cisterns (Fig. 7) and it is just here that these plaques or

FIG. 7.—Encephalogram in a case of tuberculous meningitis showing block at the tentorial opening. Note large collection of air in the basal cisterns.

clusters of basal calcification develop. Their position also corresponds well with the site of the most dense exudate found at necropsy in fatal cases of tuberculous meningitis.

There was a much higher incidence of calcifications (Table 5) in patients who were in the intermediate or advanced stage of meningitis (13 of 15) than in those who were in the early stage (four of 10). If intracerebral calcifications alone were taken into account, then no significant difference was found between patients in the three stages. If, however, only the basal calcifications were considered, then the differences were striking. No basal calcifications were seen in any of the 10 early cases, but they were detected in 11 of the 15 children in the intermediate and advanced stages. This observation again corresponds well with encephalographic studies (Lorber, 1951a) in which it was shown that in early cases obstruction of the cerebrospinal fluid pathways and tentorial blocks only rarely develop, whereas they may be found in over half of the intermediate and in almost all the advanced cases. In this connexion it is of interest that one of our patients in the early stage of meningitis recovered but later died of tuberculous bronchopneumonia. In this patient no basal exudate was found at necropsy.

There was only slight correlation between intracranial calcifications and the presence of neurological sequelae. Excluding deafness in two children, which may have been due to streptomycin, six of the 25 patients had physical or mental lesions. Intracranial calcifications were found in three of four who had hemiplegia, and in one of the other children with residual abnormality. Of the 19 patients who made a complete functional recovery only 12 developed intracranial calcifications. The basic data patients are presented in Table 6.

TABLE 5

INTRACRANIAL CALCIFICATIONS IN RELATION TO STAGE OF MENINGITIS ON ADMISSION

Stage of Disease	Total No. of Patients	Patients with Calcification		
		Basal	Cerebral	Total
Early*	10	0	4	4
Intermediate ..	11	9†	3†	10
Advanced	4	2	1	3
Total	25	11†	8†	17

* Including five patients who developed meningitis while being treated for miliary tuberculosis.

† Includes two patients with both basal and cerebral calcifications.

TABLE 6

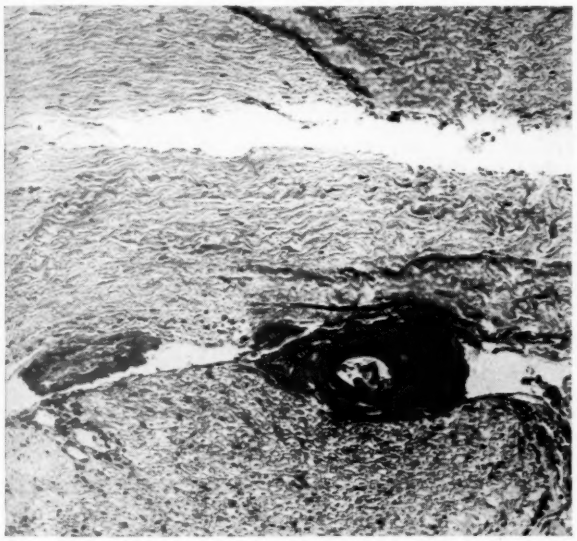
BASIC DATA RELATING TO 25 PATIENTS IN THE PRESENT INVESTIGATION*

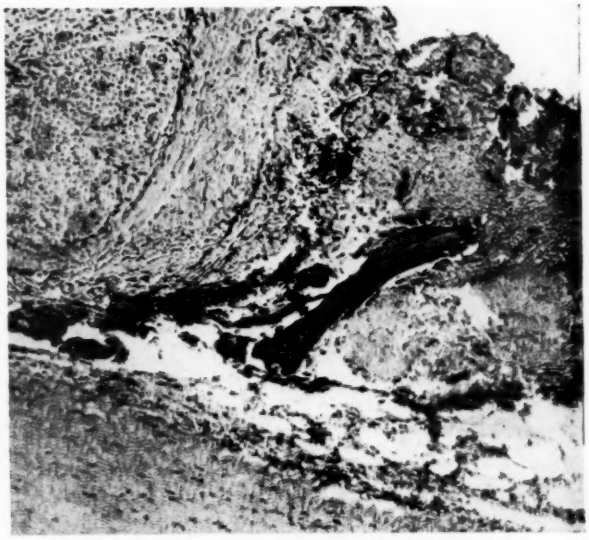
No.	Sex	Age on Admission	Stage of Disease† on Admission	On March 30, 1952		First Appearance of Intracranial Calcification (months after admission)	Site and Type of Intracranial Calcification
				Length of Observation (months)	Sequelae		
1	M	6½	I	54	None	27	(1) In frontal lobe; (2) basal, above sella
2	F	5½	E	53	None	—	—
3	M	15/12	E†	51	None	—	—
4	F	6	I	50	Deaf	35	Basal, behind sella
5	M	3	I	48	None	36	Basal, above sella (Fig. 4)
6	M	11/12	E†	48	None	36	In occipital lobe (Fig. 2)
7	F	8	E†	47	None	34	In parietal lobe
8	F	5½	I	46	None	19	(1) In area of midbrain (Figs. 5 and 6); (2) massive basal (?cisterna ambiens); (3) falx
9	F	16/12	E†	46	Deaf	—	—
10	F	8	I	44	None	29	In ?parietal lobe (Fig. 1)
11	M	20/12	A	43	Moderately retarded	42	(1) Basal, behind and above sella; (2) falx
12	F	7½	I	42	None	31	Basal, above and behind sella (Fig. 3)
13	M	13/12	A	41	Hemiplegia; retardation	—	—
14	F	10	I	40	None	—	—
15	F	20/12	I	40	None	27	Basal, behind sella
16	M	9	E	36	None	27	In frontal lobe
17	M	2	I	34	Hemiplegia; retardation; Fits	32	Massive basal, above sella
18	F	5½	A	34	Sexual precocity; optic atrophy	19	Two in parietal lobe (Lorber, 1951b)
19	M	10/12	E	34	None	—	—
20	F	19/12	E†	33	None	—	—
21	M	3½	I	33	Hemiplegia	32	Basal, above sella
22	M	12	I	31	None	27	Basal, behind sella
23	F	4½	E	31	None	—	—
24	F	3½	A	30	Hemiplegia	29	Basal, above sella
25	F	3½	E	30	None	19	In frontal lobe

* Survivors only.

† Patients who developed meningitis while on treatment for miliary tuberculosis. E=early. I=intermediate. A=advanced.

In our series of well over 100 cases of tuberculous meningitis treated with streptomycin all but two of the deaths took place in less than 18 months from the beginning of treatment. In the last two children calcified lesions were detected in the central nervous system at necropsy. On one child, who died 21 months after the beginning of treatment, a post-mortem radiograph of the brain showed some faint flecks of possible calcification in the region of the temporal lobe. These could not be located on slicing the brain. In the spinal canal, however, the meninges, and particularly the dura, were found to be calcified, and even ossified (Figs. 8 and 9).





FIGS. 8 and 9.—Sections of the spinal cord showing calcification and ossification of the meninges between the nerve roots.

The second late death occurred in a child 29 months after the beginning of treatment. Faint suspicion of calcification was detected on a radiograph of the skull five months before she died. A post-mortem radiograph of the brain showed a characteristic calcified shadow in the left temporal lobe. This was subsequently located by further radiographs of the brain slices and was found to be within the brain adjacent to the Sylvian fissure. Histologically it was composed of clusters of small calcified foci, but no tuberculous granulation tissue could be detected at the same site.

Discussion

The pathogenesis and the nature of the calcified shadows require consideration. Admittedly, in none of the living patients is absolute evidence available that these calcifications occurred in tuberculous lesions. The composition of this series, however, is such that it leaves little doubt that there must be a causal relationship between tuberculous meningitis and subsequent intracranial calcifications. For this reason it is unnecessary to discuss the differential diagnosis of pathological intracranial calcifications. Intracranial calcifications occur in normal persons in the choroid plexus, the pineal body, the tentorium cerebelli and the petro-clinoid ligaments, but none of these sites was affected in the present series.

Assuming that these calcifications are a sequel to tuberculous meningitis, there are four possible causes to consider. They may represent calcified intracranial tuberculomata, calcification in areas of healed tuberculous encephalitis or in areas of encephalomalacia following cerebral infarction, or in the tuberculous exudate in the meninges.

The eight intracerebral lesions which have been described in the survivors are probably calcified intracranial tuberculomata. Their size and situation correspond well with the description of the ' Rich foci ' and are quite unlike the more diffuse calcifications which occur after encephalitis or encephalomalacia. Eight living children with this type of intracranial calcifications are in perfect physical and mental health and for this reason alone it appears unlikely that the calcifications occurred in areas of encephalomalacia or past encephalitis. The approximately equal incidence of these intracerebral lesions in patients in different stages of meningitis at their admission favours the theory that these were the original ' Rich foci ' responsible for the meningeal dissemination.

The striking collection of calcifications in the anatomical situation of the basal cisterns in 11 patients leaves little doubt that in these we are dealing with a calcifying organizing exudate of the meninges. Their situation and shape corresponds exactly to the site of the maximal meningeal inflammation. It is also striking that in patients in the early stage of the disease on admission, and in whom only minimal exudate is to be expected, no basal intracranial calcifications developed. In those in the intermediate and advanced stages, and therefore with more basal exudate, subsequent calcifications were almost the rule. The calcification and ossification of the spinal meninges in one child who died after a protracted illness demonstrated histologically that meningeal calcification is possible after tuberculous meningitis.

Areas of extensive encephalomalacia are frequently found in fatal cases of tuberculous meningitis, but in this group of 25 survivors the only patients who are likely to have such encephalomalacia are the four with residual hemiparesis. Calcifications were detected in three, but in all three these were basal. It seems, therefore, that calcifications in areas of encephalomalacia did not occur in patients in the survivors of the present series, but probably did so in Koch's (1951) patient, who had hemiplegia on the opposite side of the body. The calcifications found at necropsy in the child who died after 29 months of treatment probably also represent calcifications in a previously infarcted area.

The only remaining problem to be considered is the prognostic significance of calcifications following tuberculous meningitis. In a very large series of 548 cases of tuberculous meningitis, treated at various centres with streptomycin, only one patient died of tuberculous meningitis more than two years after the onset of meningitis (Lorber, to be published). It would be tempting, therefore, to ascribe this favourable late prognosis to the calcification of lesions which might otherwise presumably act as potential foci of reinfection of the meninges. Such an explanation, however, is unlikely to be true. Cases have been described where calcified tuberculomata were present at the time of the onset of tuberculous meningitis and in others calcified tuberculomata were discovered long before the onset of fatal tuberculous meningitis (Tables 1 and 2). Further, the radiological demonstration of one or more calcified tuberculomata does not exclude the presence of other, non-calcified lesions, nor does it exclude the presence of caseous material in the calcifying lesions.

To conclude, it is estimated that in England alone approximately 300-400 patients are now cured annually of tuberculous meningitis. Should intracranial calcifications eventually develop in approximately two-thirds of these then tuberculosis may soon become one of the commonest causes of intracranial calcifications.

Summary

In a series of 25 consecutive children who have recovered from tuberculous meningitis and have been observed for two and a half to four and a half years 17 developed radiologically demonstrable intracranial calcifications. Most of these calcifications (13 of 17) were detected between two and three years after the onset of meningitis.

In eight the calcified foci seemed to be within the brain substance, and these were found in approximately even proportion in children in various stages of meningitis at the beginning of their treatment.

In 11 children plaques or clusters of calcification developed in the anatomical situation of the basal subarachnoid cisterns. These are considered to be calcifications in the meningeal exudate at the base of the brain. They were not found in any of the 10 children who were in the early stage of the meningitis on admission, but were present in 11 of the 15 who were in the intermediate or advanced stage.

No definite correlation was found between the incidence of intracranial calcifications and the presence of neurological sequelae.

In one child, who died of tuberculous meningitis after 21 months of treatment, calcification and ossification of the spinal meninges were found at necropsy. In an other child, who died 29 months after the beginning of treatment, a calcified intracerebral focus was found at necropsy.

The nature and pathogenesis of the calcified lesions are considered.

I wish to thank Professor R. S. Illingworth for his criticism, Dr. T. Colver for permission to investigate two of his patients, Dr. J. L. Emery for the pathological data, Dr. T. Lodge and Sister Mallinder for the radiographs, Mr. A. Tunstill for the photographic reproductions and Mr. A. F. Foster for the line drawings.

I wish to acknowledge a grant from the Tuberculosis Research Fund from the University of Sheffield which defrayed some of the costs incurred in preparing this paper.

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Addendum

At the time of correcting the proofs of this paper basal intracranial calcifications were detected in one more child within this series (Case 13—an advanced case) 47 months after his admission. Thus all four patients with hemiplegia showed calcified intracranial shadows.

There has been no significant change in the other patients and the period of observation now ranges from a minimum of 38 months to a maximum of 62 months from the beginning of treatment.

FATIGUE FRACTURE OF THE FIBULA IN CHILDHOOD

BY

ALAN L. GRIFFITHS

From the Royal Belfast Hospital for Sick Children

(RECEIVED FOR PUBLICATION MAY 3, 1952)

Fatigue, or stress, fractures have been described as occurring in many situations and at widely differing ages from 15 months to 64 years. Most have occurred in young adults, particularly soldiers in training and athletes. Although fatigue fractures usually occur in weight-bearing bones, in particular the metatarsals and tibia, they also occur in the fibula, and have even been described in the first rib and in the ulna.

The distinction between fatigue fractures and all other varieties of fracture arising in the absence of direct trauma has been clearly made by Blair Hartley (1943). Jackson Burrows (1948) in a comprehensive article, reviewed the literature of fatigue fracture of the fibula. In it he discussed the relationship between intensity and duration of stress. He described how stress of adequate intensity acting once produces a traumatic fracture, whereas a recurrent stress of much smaller intensity produces a fatigue fracture, and suggested that types intermediate between these extremes also occurred.

Fatigue fractures have been reported in several situations in children. Roberts and Vogt (1939) described a series of tibial fractures, the youngest child being 4 years old. Blair Hartley's (1942) series also included several children with tibial fractures. ' March ' fractures also occur in children. Three cases were reported recently by Macpherson (1951), and during the year in which I collected these fibular fractures I saw six metatarsal fractures in five patients of ages ranging from 5 to 10½ years.

Siemens (1942) described a case of bilateral fatigue fracture of the middle third of each fibula in a boy of 15 months. Ingersoll (1943) described three cases in boys of 9 years, ascribing the lesion to the stress of learning ice skating. Fractures in one of his cases were bilateral. Siemens quotes Brandt as having done a biopsy on a girl of 10 years with a periosteal bony thickening above the lateral malleolus. In the absence of a history of injury he considered the case to be in the nature of a stress fracture.

The following eight cases were also in children, and show a number of points which may throw a little light on this interesting condition.

Case Reports

Case 1. Joseph M., aged 4½, was brought to the hospital on July 20, 1950, because he had been limping with his left leg for the previous three weeks. He would not admit to having sustained any injury. Tenderness over the lower third of the left fibula and pain on everting the foot were found on examination. The absence of fever, malaise or muscle tenderness was noted. A radiograph showed a transverse band of increased density extending across the fibula just below the junction of the middle and lower thirds. A narrow line of diminished density was present in the centre of this band on the lateral and posterior aspects. It extended out into a cloud of callus which surrounded the bone at this level and spread up and down the shaft. The amount of callus was greatest on the lateral side, where it tended to fill up the concavity of the bone. This was considered to be a ' greenstick ' fracture of the fibula, and was treated by immobilization in a short leg plaster for a month. A second radiograph on August 3, taken through the plaster, showed a considerable increase in the amount of callus.

He did not attend after removal of the plaster until February 7, 1951, when he was brought up on account of a limp of five days' duration. This time the right leg was affected but once more there was no history of injury. He was tender over the fibula, and apyrexial. No bony changes were seen in the wet film of the fibula; so he was thought possibly to have sustained a bruise and treatment was not considered necessary. He returned nine days later, and was found to be exquisitely tender over the lower right fibula, but still apyrexial. The radiographs of the left fibula taken seven months previously were now seen, and the dissimilarity from a greenstick fracture remarked. A suspicion that the earlier fracture had been a fatigue fracture and that he now had a similar lesion in the other leg was supported by re-examination of the film taken nine days previously. On close inspection a small ' crack ' could be seen in the lateral and posterior aspects of the right fibula in the upper part of its lower third. This was most clearly seen in the antero-posterior view, where a small haze of

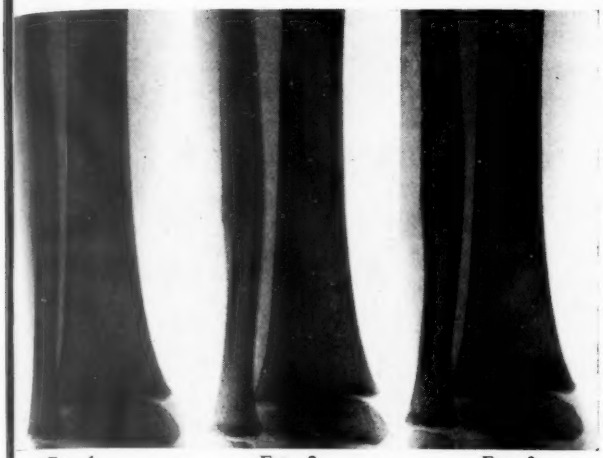

FIG. 1 FIG. 2 FIG. 3

FIG. 1.—Right fibula two weeks after onset. Callus is now clearly visible (Case 1).
FIG. 2.—Right fibula four weeks after onset (Case 1).
FIG. 3.—Right fibula eight weeks after onset (Case 1).

callus was visible to the lateral side of the bone, with a central clear area opposite the crack in the cortex. A very faint band of increased density could be seen extending across the bone at this level. A new radiograph of this leg now showed a considerable increase in callus formation on the lateral concavity of the bone extending beyond its anterior and posterior margins, with a small central translucent area corresponding to the gap previously seen. The transverse band of sclerosis was more prominent, extending upwards as it ran forwards and medially. A short leg plaster was applied, and removed after a month. Because the child complained of pain it had to be re-applied a week later for a further 10 days. Serum calcium and phosphorus levels were normal; serum alkaline phosphatase was 20 King-Armstrong units. The leg was radiographed at intervals. The callus increased in amount and density. The band of sclerosis first increased in density and then gradually disappeared. The 'crack' became broader and then assumed an irregular cystic appearance before disappearing. Finally on May 3 the bone appeared normal apart from residual thickening of the cortex on the lateral side. The fibula remained slightly tender for about three months until this date, but this is perhaps explained by his conduct.

He was a particularly robust, healthy-looking child. His mother told me that he was a very active boy, who had been doing a lot of jumping in emulation of a strip cartoon character called 'Superman'. This took the form of jumping off stairs and furniture with a cloak around his shoulders. Moreover, this had continued even after immobilization in plaster, and accounted for the badly damaged state of his plasters which had required repair or renewal at each attendance. He had rather mobile ankle joints, with one inch separation of the malleoli when the knees were together. His shoes were badly worn on the inner side of the heels.

Case 2. Patsy H., aged 5 years and 2 months, was referred to us on March 30, 1951, on account of a swelling at the junction of the middle and lower thirds of the right fibula. She gave a history of pain and a limp since being kicked on the outer side of the leg by a little girl two weeks previously. Examination showed a tender swelling over the lower right fibula. A radiograph showed a cuff of callus surrounding the upper part of the lower third of the bone. This was heaped up on the lateral aspect opposite a broad, poorly defined area of slightly denser bone containing a central transverse line of rarefaction. A short leg plaster was applied. When removed on April 17 some tenderness over the fibula was still present. A radiograph now showed that the callus had grown denser and the line of rarefaction more conspicuous. The resemblance between the x-ray appearances of this and the previous case was now remarked, and this was thought to be another fatigue fracture.

Her shoes were found to be worn to the uppers at the inner side of the heel. When questioned about unusual activity, her mother informed us that the child was learning to skip, and spent a lot of time jumping up and down.

At this attendance, four and a half weeks after the onset of symptoms, the blood calcium, phosphorus and phosphatase levels were found to be normal.

A viscopaste bandage was applied, and she was seen again a week later. Tenderness was still present, but she had continued to skip. When asked to jump, it was noticed that she did so with her feet flat, instead of springing from her toes. This flat-footed jump provoked careful observation of the local children, and it was realized that up to the age of 6 to 7 years most children jump in this way. She was still tender when seen again a fortnight later, so a 3/16 in. inner raise of the heels of her shoes was prescribed. A radiograph on May 8 showed a greater density of callus. The zone of rarefaction had expanded to a broad band, with a zone of increased density on either side. She did not attend again.

FIG 4. FIG. 5a FIG. 5b

FIG. 4.—Right fibula. Antero-posterior view two weeks after onset (Case 2).
FIGS. 5 and 5a.—Right fibula: antero-posterior and lateral views eight weeks after onset (Case 2).

Case 3. George L., aged 3 years and 4 months, was first seen on April 5, 1951, complaining of pain in his left leg and a limp following a fall two days before. He was tender over the lower fibula. A radiograph showed a narrow band of diminished density, running in an irregularly transverse line across the fibula towards the upper part of the lower third. This extended out into a cloud of callus surrounding the fibula, and had above and below it a well marked zone of increased density which also extended across the callus. This was diagnosed at the time as a healing fracture, unrelated to the recent injury, and no treatment was advised. When seen again five weeks later he was reported to have limped for a fortnight but had had no trouble since. A radiograph on May 11 showed a dense layer of callus surrounding the bone. The transverse zone of translucency no longer extended into the callus, and was wider and more irregular. The zones of sclerosis had almost disappeared. It was now realized that this was another fatigue fracture. No abnormality of feet or legs was found apart from some laxity of the ankle joints. He was wearing a pair of flat sandals too large for him, but at the relevant time had been wearing a pair of worn boots. Unfortunately, his mother could not remember on which side they had worn.

He had always had adequate cod liver oil and orange juice.

This was another child who played 'Superman', jumping off the furniture with a cloak around his shoulders.

Case 4. Unfortunately the notes on Jim B., aged 5 years, are scanty, and I did not see him personally at any time as he did not return after his first visit. He was sent up to be seen on April 20, 1951, on account of pain and tenderness over the lower end of the left fibula. There was no history of injury. A radiograph showed a faint sleeve of callus surrounding the fibula obliquely in its lower third, higher on the antero-lateral aspect. A minute nick was just visible in the callus on the lateral aspect. He was considered to have a 'slight periostitis', and adhesive strapping was applied to the ankle. The patient was told to return in one or two weeks, but did not attend.

Case 5. Barbara D., aged 5, first attended on April 21, 1951, with a history of pain over the outer side of the left leg of two weeks' duration, sufficiently severe to make her limp at times. She could not remember any injury. There was tenderness over the junction of the middle and lower thirds of the fibula. A radiograph showed a faint transverse line of diminished density running across the fibula in the lower part of its middle third. On either side of this line the bone appeared slightly more dense. A small amount of callus was present on the posterior and lateral aspects of the bone at this level. This was recognized to be a stress fracture by Mr. J. A. W. Bingham. A viscopaste bandage was considered sufficient treatment. When seen again a fortnight later she had had no further pain so the bandage was removed. No abnormality of feet or ankles was found and no history of predisposing stress or injury could be obtained. The mother remembered that the shoes she had been wearing had been badly worn, but could not recall where. A radiograph on May 5 showed an accentuation of the changes seen previously. She was asked to re-attend bringing her worn shoes, but did not come.

Case 6. Margaret S., a little girl, aged 2 years and 2 months, was first seen on May 25, 1951. She had been pushed by an older child and had fallen off a nine-inch step, landing on her right hip on a tiled floor. That evening she began to limp. Two days later she complained of pain in the right lower leg and was brought to the hospital. There was tenderness over the lower right fibula. A radiograph showed a very small amount of callus extending along the lateral concavity of the fibula with a minute nick in it just above the junction of the middle and lower thirds. The shaft of the bone showed no abnormality even when magnified. A short leg walking plaster was applied for six weeks. A radiograph on July 6 showed a considerable increase in the amount and density of callus, and an irregular oblique line of decalcification crossing the bone. The child had been wearing shoes with a built-in inner raise only slightly worn on the postero-lateral aspect of the heels. There was no history of jumping, skipping, or other stress. Adequate amounts of cod liver oil and orange juice had been taken. She was seen again on October 3 complaining of poorly localized pain in the other leg and foot of two days' duration. There was no tenderness and a radiograph showed no abnormality in the leg or foot. Three weeks later she was reported to have had no further pain but was not radiographed.

Case 7. Elizabeth McA., aged 8 years, attended on July 16 complaining of pain in the left leg. Twenty-four days previously a motor cycle had fallen on the outer side of her left leg causing considerable bruising. She had had pain causing a limp which had eased somewhat after two days and then remained steady. Examination showed a very tender swelling extending for four inches over the lower third of the leg on the outer side. There was pain on forced inversion but none on eversion. A radiograph showed a faint layer of callus to the lateral side of the lower third of the fibula and an even fainter cloud on the anterior aspect lower down. The callus appeared to be in two layers with a slight notch in the outer one. The fibula itself showed a rather doubtful suggestion of a very oblique line of translucency. This child had always been awkward on her feet, so that her father had nicknamed her 'Feet'. She had been skipping a lot before the accident and her mother had noticed that she jumped flat-footed. Her shoes were not badly worn. She was still tender when seen a week later, but was limping less. She did not attend again and no further radiographs were obtained.

The following case was found when checking the x-ray reports for the year. I did not see the case.

Case 8. Maeve R., aged 3½ years, fell and injured her left ankle. She attended hospital a week later on July 5, 1950, and was found to have marked generalized tenderness but no swelling. A radiograph (only one view available) showed a transverse crack extending

through a deposit of callus and into the fibula, 2⅛ in. from the lower end. The disproportionate amount of callus present at one week does not appear to have been commented upon.

Differential Diagnosis

The differential diagnosis between fatigue fractures in general and pathological and pseudo-fractures has been clearly stated by Blair Hartley (1943). The conditions found in children in which pseudo or pathological fractures occur are rickets, the coeliac group of diseases, renal rickets, osteogenesis imperfecta and fragilitas ossium, tumours and cysts of bone, and following severe osteomyelitis. In these the diagnosis should present no difficulty owing to the abnormal radiological appearance of the bone and the presence of systemic disease.

Acute osteomyelitis is unlikely to be mistaken for a fatigue fracture, for in the one case the patient is ill and febrile and in the other is healthy and apyrexial, even though the degree of local tenderness may be comparable (Case 1).

Low-grade osteomyelitis or periostitis is less easy and more important to differentiate, for several cases are reported which have had unnecessary operations for fatigue fracture. When the fracture line is visible running through callus or cortex or through both the diagnosis is obvious, providing it is recognized that the condition does occur. When it is absent there may be a faint transverse line of rarefaction with a faint zone of increased density on either side, or there may be a broader single band of sclerosis. There is fusiform laying down of callus both on the inner and outer surfaces of the cortex, often on one side of the bone only. In low-grade osteomyelitis the lesion in the cortex tends to appear rounded or oval rather than linear, and there is a tendency for the subperiosteal new bone to extend more widely in an irregular manner.

Differentiation from sarcoma is likely to be difficult only if the appearances of a stress fracture are not recognized, and in a very early case with minimal x-ray changes. The regular line of osteoporosis and the smooth outline of new bone with no spicule formation are against a sarcoma. A repeat radiograph after a week will accentuate this difference.

Precipitating and Predisposing Factors

Fatigue fractures appear to be precipitated by unaccustomed duration of a stress which may have been met with previously in normal life. The association of walking or marching with the metatarsal fracture is well known. Fractures of this type in femur, tibia and fibula have been associated with other aspects of military training (Bingham, 1945; Kitchin and Richmond, 1945; Richmond, 1945). Runners and jumpers appear to be prone to fibular lesions (McPhee and Franklin, 1946; Weaver and Francisco, 1940; Ronald, 1945; Asal, 1936). Other factors must also operate, however, for while not all people subjected to apparently identical stress develop lesions, a few seem especially prone. In them two or even three bones may successively display fractures. A number of predisposing factors have been recognized in relation to the metatarsal fractures such as metatarsus atavicus. My cases are too few to be significant, but some inferences may be drawn.

The precipitating factor in Cases 1, 2 and 3 was almost certainly persistent jumping. I suggest that the predisposing factor in Case 1 was his shoes, which were badly worn on the inner side of the heel. Delay in repairing these shoes had accentuated the results of faulty posture. The worn shoes may have been a major factor in Case 2 also, and possibly in Case 3. This wearing at the heel was equivalent to a half inch outer raise, so that even when standing, there was an eversion strain on the ankle. Older children normally jump so as to land on their toes, but up to the age of 5 or 6 years, and in some cases to a still later age, children land with their feet flat, taking much of their weight on the heels. Case 2 was seen to jump in this manner and Cases 1 and 3 probably did likewise. In these cases, therefore, a very considerable eversion strain must have been thrown on the fibulae. This mechanism, however, cannot apply in Case 6, where the inner raise in the shoes tended to cause an inversion strain. Professor H. A. Harris describes a rapid development of the calf muscles at 7 years of age. This would correspond with this change in method of jumping. Professor Harris also describes the evertors of the foot as having a period of rapid growth. This occurs at about 18 months of age and must exert new stresses on the fibula. This may have a bearing on Siemens's case in an infant of 15 months.

The fibulae of my cases appear more strongly curved than many of those illustrated by other observers. They show a lateral concavity with the apex of the curve in the upper part of the lower third or lower part of the middle third. This apex only sometimes appears to correspond with the site of the fracture. The curve is absent or even reversed in Ingersoll's cases, and is not marked in Siemens's case. Possible reasons for this appearance are: (1) The curve is accentuated by different positioning in the radiograph. (2) The curve is due to active or previous rickets; there is no activity as

judged by the two blood phosphatase estimations, and the epiphyses appear normal, and in two of the cases it was specifically stated that adequate vitamins had been taken. (3) Some infants have strongly curved tibiae concave medially at birth which gradually straighten. This straightening could conceivably cause curvature of the fibulae with resultant weakness. The curve may be due to the more rapid growth of the fibula than of the tibia which occurs in later foetal life. This curve is not due to trauma; it is present in normal controls and in the normal leg of Case 6.

The Role of Trauma

I suspect that, paradoxically, trauma (as distinct from stress) may play a part in the appearance of some fatigue fractures. It appears that fatigue fractures of the fibula may be symptomless until a late stage, provided that the precipitating stress is not unduly great. Blair Hartley (1942) has suggested that this is the case in fatigue fracture of the tibia. The fracture, for example, may be discovered by radiographs of the sound limb where there has been a similar fracture of the other leg as in Ingersoll's (1943) first case and in Siemens's case. Attention may be drawn to the fracture by a minor injury producing unduly great or prolonged pain, just as small localized bone abscesses are occasionally found in the same way. It may be also that the limp associated with the minor injury throws added stress on the fracture line, causing pain.

Since five of my eight cases have a history of injury, I must try to prove that they were not traumatic fractures. In Cases 3 and 6 there was callus two days after injury implying a rate of callus formation which does not occur even in the newborn. Even in Case 8, where the fall was a week before a radiograph was taken, the amount of callus was excessive. It is doubtful if Case 2 would have waited two weeks before attending had she been kicked hard enough to produce the fracture. In Case 7, however, the callus is rather scanty at 24 days especially when compared with a traumatic fracture without displacement at this level in a child of the same age who produced much more callus by the fifteenth day, and was quite recovered in 23 days. I feel that the fatigue fracture of Case 7 may have resulted from the stresses caused by limping. This discussion is analogous to that of Blair Hartley when describing fatigue fracture of the tibia. He suggests that x-ray changes may occur without symptoms. Moreover, five of his 14 cases gave a history of injury. The frequency with which a healthy child sustains various injuries makes it easy for an anxious parent to find a traumatic antecedent for any lesion.

Level of Fracture

No cases of fracture of the upper third of the fibula occur in this series. It would be interesting to know if the lesion occurs in this situation in children, for, as Jackson Burrows suggests, in adults it appears to be associated with jumping. In my first three cases, which seem clearly associated with jumping, the fracture is in the lower third at a comparable site with that in a case (not reported here) in which fracture was due to falling suddenly and landing on both feet. In the latter case a stress of high intensity and short duration produced a similar lesion to that in the other cases where a similar but recurrent stress was acting at less intensity over a longer period.

Fatigue fractures seem to occur rarely in the middle third of the fibula. This is the situation in two of my cases (5 and 6) but to group them separately would be arbitrary. It may prove more useful to group them as occurring in the third quarter of the fibula to separate them from the cases with fracture low down near the syndesmosis. However, any system of classification can only be arbitrary until the precise aetiology has been determined. Fractures of the lower third occur in two main groups as pointed out by Jackson Burrows. The first occurs at about the level of the tibio-fibular syndesmosis principally in 'elderly hard pressed women', but also in some runners (Weaver and Francisco, 1940; and Ronald, 1945). In the second group the fractures are situated more proximally, frequently twice as far from the tip of the malleolus. It is to this latter group that my cases belong, as do Ingersoll's cases, also in children, but the majority of cases published are in young athletes.

The site of the fracture line and of maximum deposition of callus is on the lateral side of the bone in all my cases, and is mostly towards the posterior rather than the anterior aspect. It is difficult to judge from published photographs, but Ingersoll's second and third cases appear to show most callus medially. This difference in position is difficult to explain but may be related to the straighter fibulae in his cases, or to a greater part played by rotation than eversion stresses. In Siemens's case the callus appeared on the lateral side of the fibulae.

Summary

Eight cases of fatigue fracture of the fibula are described and compared with other cases in the

literature. All my cases occurred between the ages of 2 years 2 months and 8 years.

It is suggested that strongly curved fibulae and badly worn shoes may predispose to the development of fatigue fractures in the fibula, and jumping and skipping act as precipitating stresses.

The site of fracture associated with jumping is at a different level in children from that found in young adults.

The diagnosis should not be difficult if the condition is known to occur.

I should like to thank Mr. H. P. Hall, Mr. J. A. W. Bingham, Mr. I. Fraser and Mr. J. S. Loughridge, surgeons of the Royal Belfast Hospital for Sick Children, for permission to publish their cases. I am also indebted to Mr. H. Jackson Burrows, Mr. I. D. Kitchin and Mr. D. A. Richmond for their assistance with the literature.

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DEGENERATIVE CHANGES IN THE LEFT LOBE OF THE LIVER IN THE NEWBORN

BY

JOHN L. EMERY

From the Department of Pathology, Children's Hospital, Sheffield

(RECEIVED FOR PUBLICATION MAY 2, 1952)

The liver in a newborn child at necropsy occasionally shows a marked difference between the left and right lobes. The left lobe is darker in colour than the right and gives the impression of being shrunken. The division between the dark and light zones lies to the right of the anterior ligament and follows an irregular line from the inferior vena cava obliquely across the upper surface of the liver to the tip of the gall bladder (Figs. 1, 2, and 3). This communication is concerned with the incidence and possible cause of this condition.

FIGS. 1 and 2.—Photographs of livers at necropsy showing dark discoloration and shrinkage of the left physiological lobe.

FIG. 1.

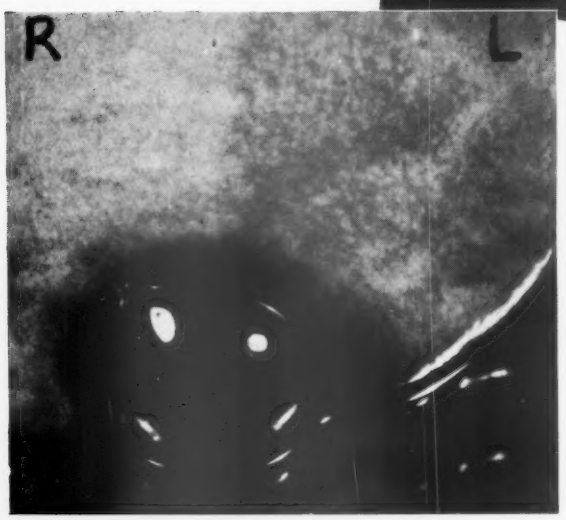

FIG. 3.—Photograph of the anterior edge of liver with unilateral congestion and degeneration showing the line of division between the affected and unaffected segments leading to the gall bladder. (approximately ×2).

FIG. 3.

FIG. 2.

Material and Methods

The livers have been used from 110 consecutive and personally conducted necropsies carried out on children under the age of 2 months. Particular care was taken not to compress or disturb the liver during its removal from the body.

Blocks were taken from the left and right lobes in a set manner (Fig. 4) and carried through fixation and other processes together, the tissue from each side thus being a control for the other.

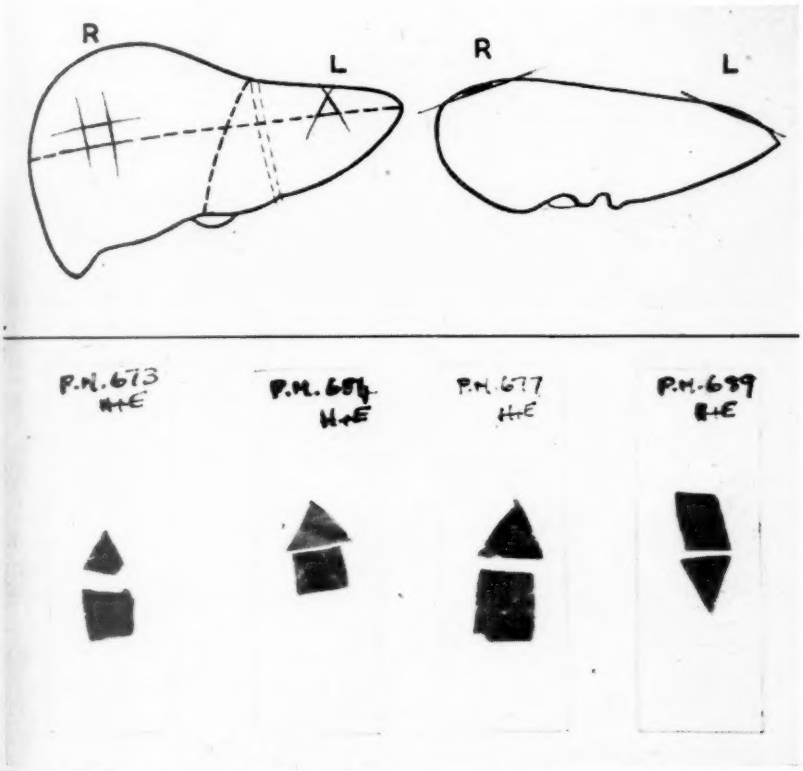

FIG. 4.—Diagram to illustrate the method of taking samples for microscopy from the liver and the method of mounting and identification of sections.

After staining the degree of hepatic cellular degeneration and shrinkage with associated sinus dilatation was assessed both absolutely and relative to the opposite side.

The findings were later correlated with the age and disease of the individual cases.

Results

The children were in the following age distribution: stillborn, 12; birth to 24 hours, 20; 25 hours to 48 hours, 14; 3 days to 5 days, 15; 6 days to 14 days, 12; 15 days to 28 days, 18 ; 5 weeks to 8 weeks, 19. For simplification and analysis the first two days were grouped together, also the periods 3 to 14 days and 15 days to 18 weeks.

The histological findings in the different age groups are presented in Table 1. Fatty changes such as described by Gruenwald (1949) were seen but, not being considered relevant to the present discussion, are not recorded here.

None of the livers from the stillborn children showed asymmetrical degeneration but one showed generalized necrosis. In the other three age groups asymmetrical changes were marked, being most frequent in the first 48 hours, when 14 of 34 cases showed the lesion. In the next group, aged 3-14 days, five of 27 cases were found and in the older group three of 37 cases (Figs. 5 and 6).

In four of these 110 cases a marked naked eye difference between the two lobes of the liver was seen, the changes being much more obvious in the completely fresh material than after fixation. The line of division between the dark, shrunken segment and the rest of the liver followed an irregular line from the superior vena cava to the central point of the tip of the gall bladder (Figs. 1, 2 and 3).

Inadequate measurements of the ductus venosus were made in many cases and no attempt has been made to correlate the histological findings with the size of the ductus of the particular specimens.

In no case was thrombosis of the portal vein or hepatic vein found although many cases showed thrombosis elsewhere in the body.

TABLE 1
HISTOLOGICAL CHANGES IN DIFFERENT AGE GROUPS

Age Group	Total Cases	Cases Showing Degeneration			
		Total No.	More on Left than Right	More on Right than Left	Sides Equal
Stillborn infants ..	12	1	0	0	1
Birth to 48 hours ..	34	17	14	1	1
3 days to 14 days ..	27	8	5	3	0
3 weeks to 8 weeks	37	3	3	0	0
Totals	110	29	22	4	2

Discussion

Since the classical study of the liver by Mall

(1906) the complete division of the liver into two physiological lobes distinct from the superficial anatomical difference has been universally recognized. The lesions seen in the livers of the newborn appear to coincide with the left physiological lobe, the line of division following the physiological division between the right and left livers.

The appearance of the livers in these children is very like that of the early changes produced by Rous and Larimore (1920) when they occluded a segment of the portal vein in rabbits. The lesion in the liver is also similar to the condition described

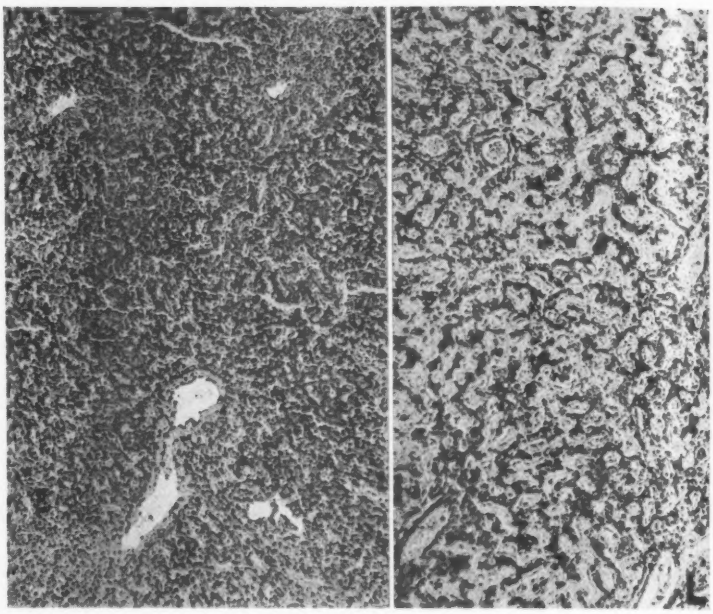

FIG. 5.

FIGS. 5 and 6.—Photomicrographs showing the different microscopic appearances in the left and right lobes from two livers. (Haematoxylin and eosin × 70.)

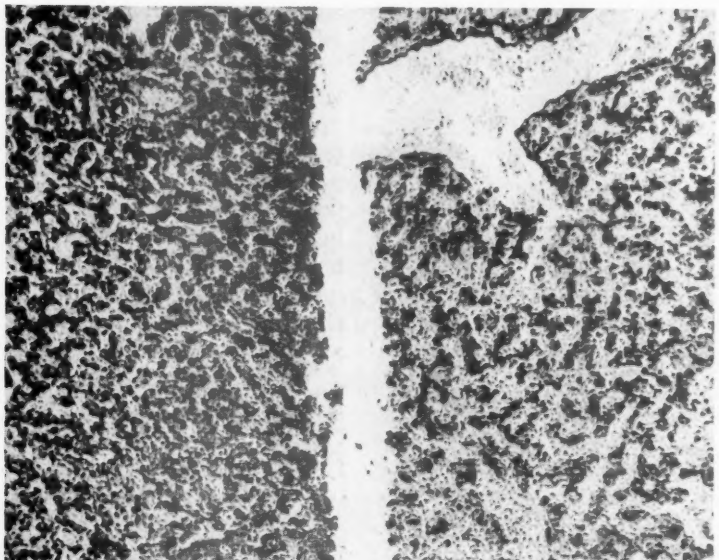

FIG. 6.

in the old German literature as the 'atrophic red infarct of Zahn', and is again similar to changes seen in animals with an Eck fistula (Winternitz, 1911). Circulatory disorders producing such lesions in one lobe of the liver in adults have long been recognized (Wassink, 1915). All these lesions seem to be the result of disorder in the blood supply to the liver. In the present study it was not found in the stillborn infants and its greatest incidence was found immediately after birth, so it seems to be directly related to a vascular change occurring at birth.

Although the blood supply to the liver varies (Grindlay, Herrick and Mann, 1941), the liver cells are normally dependent for a considerable amount of their oxygen upon the portal venous supply, only about 40% coming from the hepatic artery (Markowitz and Rappaport, 1951).

The intra-hepatic circulation of venous blood at the time of birth is illustrated in Fig. 7. One notable feature is that the ductus venosus at the time of birth has a diameter of about one-seventh that of the umbilical vein (Barron, 1944). This implies that most of the blood from the placenta perfuses the left lobe of the liver; i.e., the left lobe of the liver receives the most highly oxygenated blood of the foetus. Immediately after birth the blood supply of the left lobe of the liver has to come from the portal vein. Thus the left lobe of the liver is subject at birth to a sudden gross diminution in the oxygen content of its circulating blood, a change which does not occur in the right liver.

It will also be obvious (Fig. 7) that the blood from the portal vein going to the left will only enter the left liver provided the blood is prevented from passing directly through the ductus venosus into

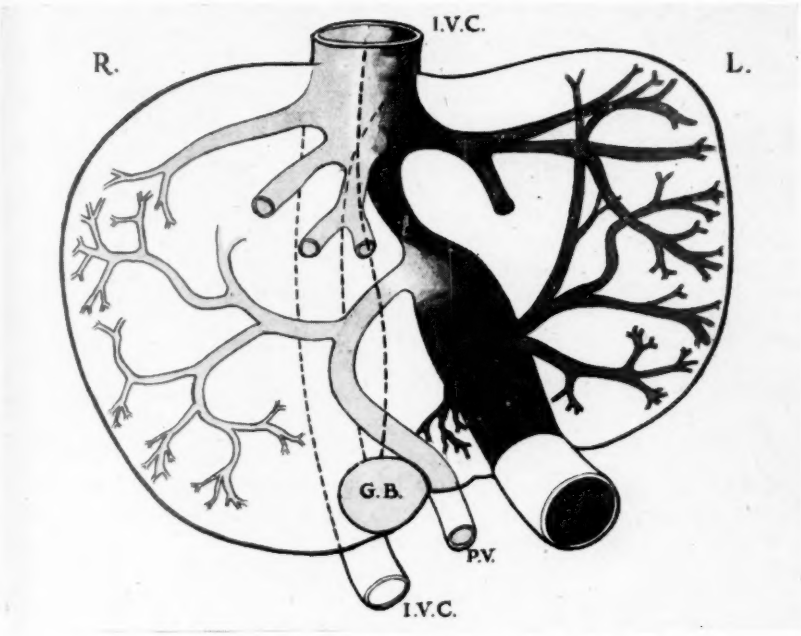

FIG. 7.—Diagram of the venous circulation of the liver at time of birth.

the inferior vena cava. Scammon and Norris (1918) showed that during the first eight days of life the ductus venosus was closed in only 2·3% of infants; that figure rose to 18% by 15 days to 37% by 22 days, to 75·7% by 32 days, and to 97·3% by the end of two months. The circulatory studies of Franklin, Barclay and Prichard (1940) and Barclay, Franklin and Prichard (1942) suggest that the necropsy appearance of a vessel like the ductus venosus will not necessarily indicate its degree of function during life. While taking this into consideration the possibility of a portal-caval shunt of a temporary nature at birth, i.e., a temporary physiological Eck fistula, cannot be ruled out, and such a condition would be expected to produce a change in the liver such as that seen in the left lobe in the present cases. Räihä (1941) showed that intravenous bilirubin is eliminated less readily in dogs with a Eck fistula, and he suggested that infantile icterus may be related to a transitory physiological fistula through the ductus venosus at birth. Clement Smith (1951) suggests that this feature merits consideration.

The parallel diminishing incidence of the degenerative changes in the left liver after birth and the patency of the ductus venosus may indicate a causal relationship but both are so closely related to birth that the coincidence may not be significant.

The lobular distribution in the liver of blood from different parts of the portal tree is a well known factor in producing asymmetrical hepatic lesions in adults but it is difficult to see how this mechanism can be active at birth.

The question that arises concerning the liver degeneration is whether the condition is to be considered physiological and reversible or pathological. The high incidence of the condition in children who had otherwise adequate causes of death suggests that the condition is generally both physiological and reversible. It is possible that under conditions of circulatory upset or in an otherwise ill child it may be a contributory cause of death. The lesion may well be itself related to the production of physiological icterus.

Summary

Degeneration of parenchymal cells with dilatation of the sinusoids of the left lobe of the liver is described in the newborn.

The lesion was not seen in stillborn infants and was most common in children dying within 48 hours of birth.

The localization of the lesion to the left physiological lobe of the liver, the age incidence, and the associated incidence of patency of the ductus venosus suggest that the condition is associated with the great physiological circulatory changes in the left lobe of the liver which occur in the newborn at the time of birth.

The photographs were taken by A. K. Tunstill.

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VOMITING OF UNCERTAIN ORIGIN IN YOUNG INFANTS

BY

B. S. B. WOOD and ROY ASTLEY

From the Children's Hospital, Birmingham

(RECEIVED FOR PUBLICATION JUNE 3, 1952)

For the past few years we have been interested in vomiting in young infants, and especially in those cases where no organic basis for the symptoms could be discovered.

Historical Note

The earlier records of vomiting in infancy, as would be expected, mainly concern infective causes and even Armstrong's (1777) description of ' pyloric stenosis ' is included in a section on watery gripes. Later, as the popularity of artificial feeding increased during the nineteenth century, this factor became prominent and Henoch (1889) remarked that improper feeding, especially over-feeding, was the usual cause of dyspepsia. At about this time it was suggested that the infant's constitution might be a contributory cause, Dewees (1834) dividing vomiting into idiopathic and sympathetic, while Rotch (1896) postulated that irritation of large sympathetic ganglia might be responsible for vomiting in some cases.

Up to the turn of the last century food and constitution were the most important diagnostic factors once infective causes had been, as far as possible, excluded. Since then, however, with the re-discovery of pyloric stenosis, the advance of surgery and the application of such aids as radiology, more and more cases of idiopathic vomiting are being recognized as having an organic basis.

Present Study

A consecutive series of 100 babies admitted to hospital under 6 months of age because of vomiting without diarrhoea was closely studied and followed up. In 82 the vomiting could be ascribed to some organic disease such as pyloric stenosis, intestinal obstruction, or infection; however, the cause remained uncertain in 18, even after a stay in hospital of several weeks (Wood, 1951).

By selection 46 such undiagnosed cases were collected over a further two years; they were examined clinically and radiologically, and followed up until their symptoms abated. Twenty-four of these 46 were considered finally to have extrinsic factors as the main cause of the vomiting, underfeeding being the commonest. This has been discussed elsewhere (Wood, 1952).

In the remaining 22 infants the vomiting appeared to be of uncertain aetiology, and it is the purpose of this communication to describe their symptomatology, to speculate on the possible aetiology, and to suggest fruitful lines of treatment.

The 22 cases seemed to fall into two sharply demarcated groups. In one the onset was gradual, the vomiting was not typically projectile but it continued for more than six months in every case. These infants are termed ' persistent vomiters of uncertain origin '.

In the second group the onset was abrupt, the vomiting was forceful, often frankly projectile, but had ceased in all the babies by the age of 3 months; they are therefore described as ' non-persistent vomiters of uncertain origin '. This method of classification is helpful as it carries a certain prognostic implication as well.

The two groups roughly correspond with Freudenberg's (1942) division into atonic and spastic vomiting.

Fig. 1 and Table 1 compare the two groups and

TABLE 1

COMPARISON OF AVERAGE DATA IN PERSISTENT AND NON-PERSISTENT VOMITING OF UNCERTAIN ORIGIN

	Persistent	Non-Persistent
Duration of vomiting	29 weeks	7 weeks
Age at lowest weight	20 weeks	5 weeks
Age at reaching expected weight	About 1 year	25 weeks
Effect of mixed feeding	Cure	None

suggest that they are different syndromes, which are therefore considered under separate headings.

Persistent Vomiting of Uncertain Origin

There were 10 cases in this group (two in 100 consecutive cases of vomiting without diarrhoea under 6 months of age).

From Table 2 certain features emerge. Most of the infants were breast fed soon after birth and therefore at the onset of symptoms, and there was little evidence of under-feeding or aerophagy. The condition seemed to progress slowly, the duration of symptoms before admission averaging nine weeks. Oesophagitis or gastritis occurred in a number as shown by blood (two cases) and mucus (five cases) in the vomit. There was little or no evidence of obstruction to the passage of food from the stomach; gastric peristalsis and upper abdominal distension were seldom seen and no pyloric tumour was ever felt by the authors.

TABLE 2
PERSISTENT VOMITING OF UNCERTAIN ORIGIN

Total number	10
Males	8
Firstborn	3
Breast fed	7
Average age	
At onset	3½ weeks
On admission	12¼ weeks
Vomiting	
From birth	5
Duration before admission	9 weeks
Projectile	4 reported, 1 observed
Content of vomits	
Mucus	5
Blood	2
Bile	1
Constipation	5
Average admission weight	85% of expected weight
'Hypertonia'	3
Aerophagy (clinical)	1
Hunger and crying after feed	3
Upper abdominal distension	2
Visible peristalsis	1
Palpable tumour	0
Average stay in hospital	5 weeks
Mortality	0
Average age at cessation of vomiting	32 weeks

The severity of the condition can be gauged by the average hospital stay of five weeks (maximum 11 weeks) and the average weight of 85% of the expected weight, the lowest being 60%.

Radiological Findings. The 10 children in this group had repeated barium studies of the upper alimentary tract. These were negative until recently, when follow-up examinations showed abnormalities in four. In these the cardia was within the thorax; there was a small loculus of thoracic stomach and gastro-oesophageal reflux occurred ('congenital short oesophagus').

Illustrative Case Histories. The following case histories illustrate certain features of the condition and its treatment.

SEVERE INTRACTABLE VOMITING. Case D had recurrent vomiting, often with altered blood, from a few days old. On examination at 15 weeks he was an alert, smiling, precocious infant, very wasted but quite active. His vomits nearly always contained large amounts of mucus. Fig. 1 shows how he began to gain weight in hospital after complementary feeding and stomach wash-outs were started. He relapsed several times, however, once so severely that he had to be put on intravenous fluids, and only ceased vomiting at about 34 weeks of age. Repeated radiographic examinations with barium were negative until at the age of 4½ years a small gastric loculus was demonstrated to lie above the diaphragm.

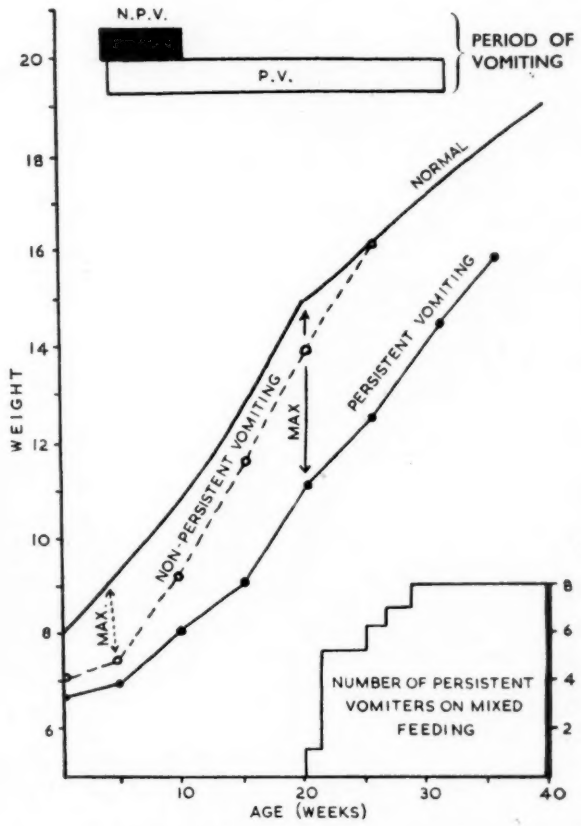

FIG. 1.—Weight chart of Case D showing the prolonged duration of the vomiting and the cure with mixed feeding. The upper line indicates normal expected weight; he had not reached this by his first birthday.

IMPROVEMENT WITH THICK, HIGH-CALORIE FEEDS. Case No. 47 was a twin whose brother had had pyloric stenosis treated by Rammstedt's operation. He started to vomit at about 10 weeks of age and was admitted two weeks later for laparotomy as a case of suspected pyloric stenosis. A barium meal was normal. At operation no tumour was found and he continued to vomit afterwards, although the pyloric muscle had been incised. When he was discharged he was offered a very thick, high calorie cornflour feed of about 30 calories per ounce. His vomiting continued unabated but his weight rose and in fact equalled that of his twin 'pyloric' brother, who was not vomiting but receiving a more normal food intake.

Aetiology. The similarity between these cases of persistent vomiting of uncertain origin and mild cases of gastro-oesophageal incompetence associated with a partial thoracic stomach includes the features of onset soon after birth, haematemeses, intermittent progress and great improvement on introducing mixed feeding. Indeed, four of them, despite repeated negative radiological findings on previous occasions, are now found to have a small, partially thoracic, stomach.

It is possible that these four were examples of sliding herniae, sometimes present, sometimes reduced, or even that the vomiting itself led to the development of such herniae in the course of time.

It is perhaps more likely that the anatomical abnormality was present throughout life but that the x-ray examination failed to reveal it because at the time of examination gastro-oesophageal reflux was absent or minimal; when fluoroscopy happened to coincide with the presence of reflux the abnormality became apparent.

In the absence of reflux it is sometimes very difficult to demonstrate that the terminal portion of the gullet is really stomach. The barium tends to pass from the oesophagus in a stream of constant width that fails to distend the often tiny loculus of thoracic stomach. There may be no constriction at the site of the cardia; the hiatus and the gastro-oesophageal angle may appear normal. It is often only when reflux is induced that the barium fills the thoracic stomach completely, showing its size, its often asymmetrical situation relative to the oesophagus, and the site of a change of mucosal pattern. The following example may be quoted. During one examination all tests failed to provoke gastro-oesophageal reflux; hiatal anatomy and function appeared entirely normal. As the rather prolonged examination was about to be terminated as negative, the child began to cry; with the resultant raised intra-abdominal pressure, re-application of the tests for reflux immediately provoked its occurrence and revealed that the cardia lay above the diaphragm.

It is evident, therefore, that when symptoms suggest gastro-oesophageal incompetence one negative x-ray examination must be treated with reserve. Repeated examinations may be necessary to establish the diagnosis.

In the remaining six children in this group, where the vomiting is still of unknown origin, the possibility of gastro-oesophageal incompetence due to a yet undiagnosed small amount of intrathoracic stomach must therefore remain. Failing this, they are possibly mild or borderline examples of the condition of chalasia (Neuhauser and Berenberg, 1947), i.e., a lax but normally situated cardia. For reasons given elsewhere (Carré and Astley, 1952) it is thought that certainly some cases of chalasia are in fact examples of partial thoracic stomach.

Re-examination of the case records has failed to reveal any point of difference between those with and those without demonstrable anatomical defect; it would seem reasonable, therefore, to postulate the presence of a gastro-oesophageal dysfunction of some kind in all.

Treatment. These cases responded best to treatment on the lines usually adopted in gastro-oeosophageal incompetence (propping in the vertical position, increasing and thickening the feeds), while in most cases the introduction of a mixed diet cured the symptoms. The exact differentiation of the defect is therefore of less importance as the treatment seems to be the same.

'Vomiting itself is undesirable' because it 'fills attendants with gloom' (Jacoby, 1946) but it is worth recalling that none in this series died. These facts, together with a workable line of treatment, have enabled us to tackle this disorder with some degree of confidence and even of enthusiasm.

Non-persistent Vomiting of Uncertain Origin or Pseudo-pyloric Stenosis

There were 12 cases (three in 100 consecutive cases of vomiting without diarrhoea under 6 months of age) in this group. They are given some prominence because, although few, they closely resemble pyloric stenosis; on this account they are sometimes subjected to operation, as happened in five of the 12; four others were given atropine methyl nitrate ('eumydrin') for the same reason.

The summary of the findings is given in Table 3, where they are compared with those in a series of 75 cases of hypertrophic pyloric stenosis. The close similarity is apparent.

It will be seen, however, that in non-persistent vomiting of uncertain origin the children are less likely to be boys, are rarely breast-fed at the onset,

TABLE 3

COMPARISON OF NON-PERSISTENT VOMITING OF UNCERTAIN ORIGIN AND HYPERTROPHIC PYLORIC STENOSIS

	Non-Persistent Vomiting of Uncertain Origin	Hypertrophic Pyloric Stenosis
Total number	12	75
Males	8	*10**
Firstborn	7	*5½*
Breast fed	2	*5½*
Average age		
At onset (weeks)	3	*3½*
On admission (weeks)	5½	*5½*
Vomiting		
From birth	3	*1*
Duration before admission (weeks)	2½	*2½*
Projectile	7	*10*
Content of vomits		
Mucus	2	*2*
Blood	1	*1½*
Bile	0	*0·8*
Constipation	7	*9*
Average admission weight (% of expected weight)	80	85
Hypertonia	2	*2*
Aerophagy (clinical)	3	*2*
Hunger and crying after feed	3	*1*
Upper abdominal distension	5	*9½*
Visible peristalsis	5	*6½*
Palpable tumour	8	*11½*
Barium meal		
Spasm	4	
Aerophagy	2	
Mortality	0	*0·3*
Average age at cessation of vomiting (weeks)	10	

* Figures in italics are expressed per 12 cases of hypertrophic stenosis so that the two columns are directly comparable.

tend to be more fretful and cry after feeds, and, although visible peristalsis occurs nearly as frequently as in pyloric stenosis, it is not often as well marked. All these factors are of relative value only, so one is left with the 'tumour' and the x-ray appearances.

The Tumour. In our experience, and in the opinion of some of our colleagues, with whom we have discussed this problem, there is a difference in the consistency of the mass in non-persistent vomiting of uncertain origin. It is only felt at a time when the true pyloric tumour is really hard, just before or just after a vomit, and then is less well defined and softer than in frank pyloric stenosis. In addition, it relaxes quickly and, unlike a true tumour, cannot be felt again and again once it is found. In this series when a mistake occurred and no hypertrophied muscle was found at operation, the observer always in retrospect remarked that the mass was perhaps not quite typical. Such was our own finding in the two cases where we felt 'tumours' which were not subsequently confirmed; they both appeared momentarily and relaxed quickly. Even in Finkelstein's (1919) case where the tumour was felt by all who were on the ward round it was softer than usual.

Radiological Findings. Four of the 12 babies in this group, when examined by a small, food-free barium meal, presented the radiological picture we consider indicative of infantile pylorospasm.

There was narrowing of the pyloric antrum that simulated to a varying degree the direct x-ray evidence of hypertrophic pyloric stenosis. Although this narrowing persisted for periods from 10 minutes to over an hour, it lacked the absolute constancy and aperistalsis of the stenosed segment in the latter condition. Continued observation showed that eventually peristalsis began to cross the narrowing, momentarily widening it; then the segment became shorter and widened from the proximal end, so that it was more tapering in shape and finally of normal calibre (Fig. 2).

In the normal infant the pyloric antrum often takes one or two minutes at the beginning of an examination to widen to its full width, possibly as a valvular mechanism related to that present anatomically in certain lower animals (Forssell, 1923, 1939). 'Infantile pylorospasm' appears to be a retardation of this normal process and is perhaps a delay in relaxation rather than a spasm.

The narrow segment may cause considerable difficulty in its differentiation from hypertrophic pyloric stenosis; indeed, the first two instances we encountered were misinterpreted. The radiological diagnosis is considered more fully elsewhere (Astley, 1952).

Illustrative Cases. The following cases illustrate these diagnostic difficulties.

CLINICAL MISDIAGNOSIS. G, a first baby, bottle-fed from birth, was admitted to hospital at the age of 5 weeks. Vomiting had occurred from birth, but at 2 weeks it became more severe, projectile in character and contained mucus with, at times, a little altered blood. On examination she was a lusty infant within 5% of her expected weight and took her feeds well. A contractile mass was felt to harden and relax in the pyloric area towards the end of the feed on three occasions by two observers, including one of the authors. Nearly every feed was followed by an extremely forcible vomit, which was projected a distance of at least a foot and a half. At operation, however, no pyloric tumour was found and no other cause for the vomiting was discovered.

Her post-operative course was stormy as she continued to vomit explosively despite atropine methyl nitrate and then nitroglycerine (Falle, 1948). Indeed,

2 (a)

2 (b)

2 (c)

2 (d)

FIG. 2.—Case 132 showed 'pylorospasm': A, pre-pyloric narrowing simulating hypertrophic stenosis; B and C, the gradual widening of this segment over half-an-hour; D, normal appearances four days later. (Reproduced by permission of the Editor of the *British Journal of Radiology*.

after one dose of the latter drug she burst the abdominal wound because of the force of her vomiting. This exactly parallels a similar case of Rocher's (1931) which suffered the same mishap because of persistent extremely forceful vomiting after operation. After a further two weeks of intravenous feeding breast milk was offered by mouth and she began to keep her feeds down, regaining her expected weight by 21 weeks.

CLINICAL AND RADIOLOGICAL MISINTERPRETATION. *Case 81.* Vomiting began at 4 days when the baby was put on the bottle. The vomiting was projectile and contained milk curds 10 hours after her last milk feed, indicating some degree of gastric retention. A pyloric 'tumour' had been palpated by another observer and at 12 days old she was admitted for operation. Clinical examination by one of us failed to reveal a palpable pyloric tumour. A barium meal showed some pre-pyloric narrowing while, with the examining finger in that area, it was possible to palpate a soft mass which, however, did not harden to anything like the consistency of a true pyloric tumour. The stomach emptied fairly well but the narrowing of the pyloric area was constant for at least 15 minutes.

At operation no tumour was found and the normal pyloric muscle was incised. A barium meal three weeks after operation showed no abnormality and, although slower to gain weight than most, she was over 16 lb. at 6 months and had not vomited since discharge at 10 weeks old.

Aetiology. It might be argued that some of these infants are early or mild cases of pyloric stenosis where pylorospasm without hypertrophy accounts for their symptoms. No case of ours has been observed to proceed from spasm to true hypertrophic stenosis, although Uhr (1932) described such an instance. This raises the old question recently discussed by McKeown, MacMahon and Record (1951) of whether an acquired spasm can lead to stenosis, and it is apparent that much still remains to be clarified on this point. Confusion of terminology (Sauer, 1924) still exists and when one remembers that in many continental centres the diagnosis of pyloric stenosis is based on x-ray findings (which can occasionally be misleading) rather than palpation of a tumour and is rarely supported by the acid test of operation, it is possible that some of these discrepancies can be explained. From the radiological standpoint alone it is possible that some of Meuwissen and Slooff's (1934) cases were in fact examples of spasm and not of true hypertrophic stenosis.

In the present series five were operated on and found to have no hypertrophy; in the other seven the condition subsided more rapidly than is usual in true pyloric stenosis.

The question of pylorospasm was first raised by Finkelstein (1919), who emphasized its rarity,

deploring that 'English doctors call all cases of vomiting without obvious cause "pylorospasm"'. Recent British opinion has hardened against such a diagnosis. Thompson and Gaisford (1935) believed that it 'exists more in the mind of the paediatrician than in the abdomen of the child', while Field (1941) was its solitary supporter at a meeting of the Royal Society of Medicine.

In the present series the unequivocal projectile vomits containing mucus, associated with constipation, visible peristalsis, and the frequent presence of a contractile mass palpable in the pyloric area, all point to some obstructive factor. When the radiological findings and the self-limited course are taken into account the similarity to pyloric stenosis is apparent.

Including the four mentioned previously, pylorospasm has been observed radiologically in 10 babies, vomiting for a variety of reasons (Astley, 1952). The most constant factor was aerophagy, which was a pronounced feature in six (in two there were gross anatomical causes for swallowing air). It is interesting to speculate whether a reflex failure of relaxation occurs to prevent excessive amounts of air from passing into the small intestine.

It is evident that the radiological picture described is not pathognomonic of non-persistent vomiting of uncertain origin nor found in all instances of it. A reasonable attitude is to regard it not as a separate entity but as a non-specific phenomenon that may occur in this condition and cause difficulty in its radiological differentiation from hypertrophic pyloric stenosis.

In considering the possible causes for the spasm in the present series it is of interest that seven of the 12 cases had a definite history of beginning to vomit a day or so after they had been put on the bottle, and in two others (making a total of nine) such a sequence could not be excluded, the mothers' stories being indefinite; only two cases of the other 34 with vomiting of unknown origin had a similar story. A review of the literature on this point is not very rewarding although cases reported by Morse (1911), Koplik (1913), Kerley (1920) and Finkelstein (1919) had somewhat similar feeding histories. Of recent cases, Falle's patient (1948) was breast-fed but Mann and Anscombe's (1948) began to vomit on changing to the bottle. This finding may be due to chance, to mechanical differences between nipple and teat, rate of milk flow, or to difference in the milk itself.

Treatment. It seems that laparotomy (five cases), even if a modified Rammstedt's procedure (two cases) is performed, should be avoided; there was no miraculous cessation of vomiting as described by Browne (1931) and Thompson and Gaisford (1935). One case was complicated by a burst abdomen, another by wound sepsis following operation; all this argues against any laxity in differentiating between true pyloric stenosis and its imitators, and against operation on suspected cases of spasm as a form of investigation or of treatment (Mann and Anscombe, 1948; Davison, 1951). While maintaining a plea against unnecessary operation it is worth recalling that in this series, although no case of non-persistent vomiting of uncertain origin has died as a result of such an operation, two cases of true pyloric stenosis have died largely on account of delay in diagnosis and operation.

The effect of antispasmodics was disappointing, but this may be misleading on the score that only those babies who fail in 'medical' treatment tend to be admitted to hospital and our series consists mainly of hospital admissions. Nitroglycerine was used in one case in view of the experience of Falle (1948) but it had no appreciable effect. Most of these cases seemed to get better quite quickly after a few weeks and this might lead to mistaken ideas on the value of certain treatment.

Exclusion of organic disease such as true hypertrophic stenosis, preferably without operation, would seem of the first importance. As Davison (1951) has pointed out, experience is as necessary to the radiologist as to the clinician in these difficult cases.

Full calorie feeding, preferably at the breast, sedation, stomach wash-outs and perhaps the use of an antispasmodic, would seem the best means of tiding over the temporary upset. It is worth remembering that in earlier days many cases of true pyloric stenosis used to be kept alive by re-feeding after a vomit until this disease (also a self-limiting one) had burnt itself out.

Conclusions

Many explanations have been offered in the past for these obscure forms of vomiting in infants, such as hypertonia (Hess, 1914), autonomic imbalance, greed, over-activity and mucous gastritis. In this series, however, we have not been able to incriminate such factors, which are probably symptoms of the underlying starvation due to the vomiting rather than a cause of it.

We feel that in most cases of vomiting without a demonstrable organic basis the most profitable line of management is to search for and correct feeding faults (often unsuspected underfeeding); then if this does not relieve the symptoms, one is usually left with a member of one of the two groups which we have described and for which we have suggested treatment.

Summary

Vomiting of uncertain origin accounted for 18% of babies under 6 months of age admitted to hospital because of vomiting without diarrhoea. Forty-six such cases were studied.

When those cases found to be due to feeding difficulties (about half) were excluded, the remaining 22 fell into two well-defined groups termed persistent and non-persistent vomiting of uncertain origin respectively.

In persistent vomiting of uncertain origin the vomiting had an average duration of 29 weeks; normal expected weight was not regained until about the age of 1 year. Nursing in the vertical position and thickening of the feeds were effective therapeutic measures. Gastro-oesophageal incompetence is considered a possible causal factor.

In non-persistent vomiting of uncertain origin the average duration of vomiting was seven weeks; normal expected weight was regained by about 6 months of age. There were some clinical and radiological similarities to hypertrophic pyloric stenosis, but reasons are given for the belief that it is a different entity.

We are very grateful for help from Professor J. M. Smellie, Dr. C. G. Teall and the consultants of the Children's Hospital, Birmingham, and for permission to examine cases under their care. We are also indebted to Dr. Jean Mackintosh, of the Birmingham Maternity and Child Welfare Department, for help in tracing cases, and to the nursing staff of the Children's Hospital for their cooperation and constructive criticism.

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THE GROWTH, HEALTH AND FOOD OF A SINGLE INFANT

BY

NANCY B. BRANSBY and E. R. BRANSBY

(RECEIVED FOR PUBLICATION MAY 31, 1952)

This note concerns the weight, growth, health and food of a girl from the ages of 9½ to 52½ weeks.

The child, the fifth of her parents, was born on December 19, 1950. The birth was normal and the birth weight was 7 lb. 3 oz. She was fully breast fed for a few days and then partly so for about eight weeks. From one week after weaning a record was kept weekly of the food she ate, except for one spell of two weeks and two spells of four weeks. The amount of food eaten was found by weighing the tins of food at the beginning and end of the week, and by taking account of any food wasted. Foods such as egg and soup were noted in spoonfuls as eaten. The child ate little bread or rusks up to the age of 1 year; there was thus no trouble about wastage of such foods. The child was content and happy during the 43 weeks of the study, except, of course, during illness. She was in fact a model baby.

Results

Amount of Foods Eaten. The amount of milk taken was fairly steady during the whole time at about 27 oz. of full cream milk powder a week. The amount of sugar too was steady at about 6 oz. a week. Cereals were first eaten at the age of 12 weeks, the amount taken reaching 10 oz. per week at 15 weeks, which then varied from week to week with an upward trend. Bone broth was given at the twenty-fourth week, and egg and fish about the thirty-fifth week. Cod-liver oil was given from a few weeks of age and orange juice at the twentieth week. The infant was fed the amounts of food she would take. On the whole she was slow to accept new foods.

Growth. Fig. 1 shows for each week of the study the energy intakes, the weight of the infant and the gain in weight. The weight at one year was 23 lb. 7 oz., giving a gain in the year of 16 lb. 4 oz. Had she not had bronchitis in the eleventh month the weight at one year would have been about 24½ lb., giving an annual gain of about 17 lb. 5 oz. This is greater than the mean annual gain of 14 lb. 2 oz. given by Parfit (1951) and 14 lb. 7 oz. by Hammond (in press) for a group of infants in Leeds. The likely gain of 17 lb. 5 oz. in the year was one and a half standard deviations above the mean given by Parfit (1951).

Table 1 shows the infant's weight gains in spells of four weeks and those found by Hammond. Progress was slow up to 16 weeks due to poor gains during the time of breast feeding, but by 20 weeks progress was just above normal; then for a few weeks it was rapid. Her weight gains in the four quarters (13 weeks) of the year and those found by Parfit (1951) are given in Table 2a. The third quarter was a time of very rapid gain.

The 43 weeks under review fall into three phases of growth, namely: (1) steady progress, a gain of 8½ oz. a week between February 24 and May 19, that is, from the age of 9½ weeks to 21½ weeks; (2) rapid progress, a gain of 9 oz. a week between May 26 to July 14, that is, from the age of 22½ weeks to 29½ weeks, after a loss in weight of 9 oz. in one week due to about seven days of diarrhoea and vomiting; and (3) steady but reduced progress, about 4 oz. a week, from July 14 to November 24, that is, from the age of 29½ weeks to 48½ weeks, after which there was a loss in weight due to bronchitis.

The slower rate of gain in weight in (3) was partly due to the child becoming more active. About the middle of July she was put to kick on the floor, and by the end of the year she was crawling quite well.

The infant was ill five times during the study. A cold in March, mumps in April and a cold in October were slight, while diarrhoea and vomiting in May and bronchitis in December were more severe. Each illness had an effect on growth. Thus, the gain in weight was less than it had been

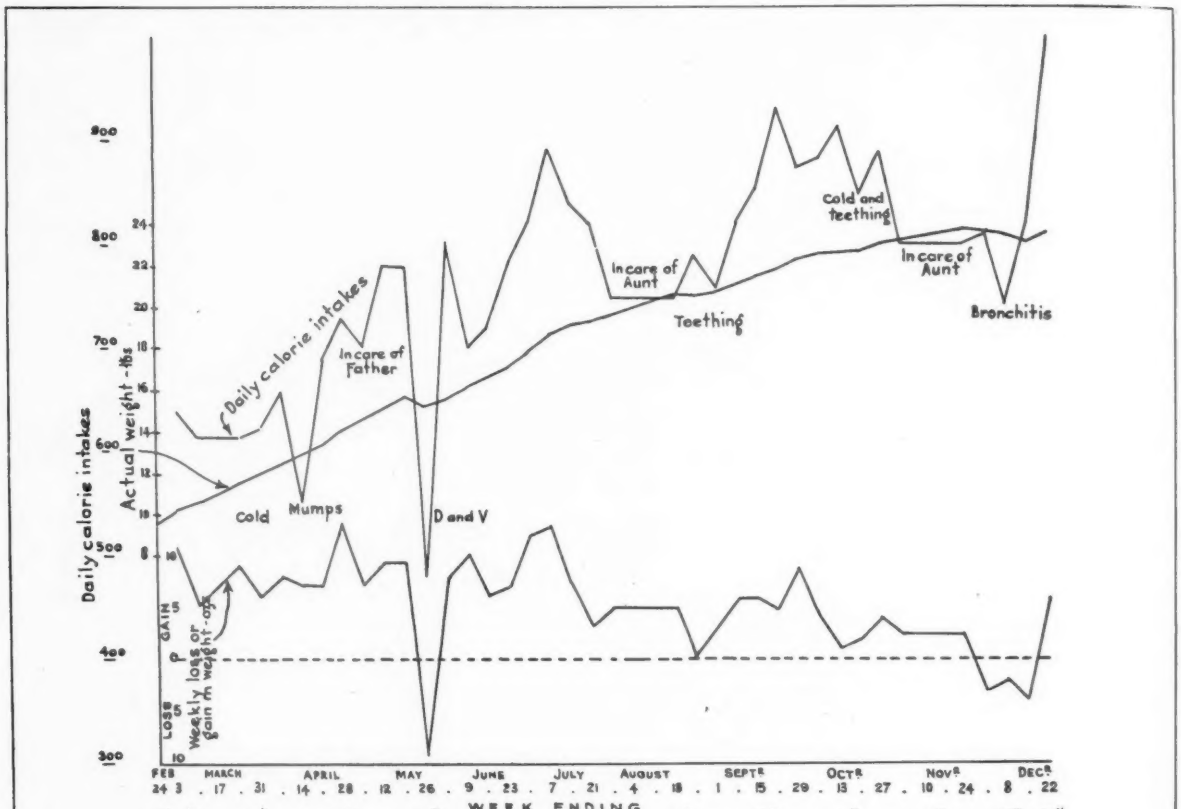

FIG 1: Calorie intakes, weight (lbs) and weekly weight gains (oz) from the age of 9½ to 52½ weeks.

by about 2 oz. a week due to the first cold, during mumps by about 1 oz. a week and during the second cold, when she was teething, by 2 to 3 oz. During the bout of diarrhoea and vomiting there was a loss of 9 oz. in one week, and again a loss of 9 oz. in three weeks due to the attack of bronchitis.

TABLE 1

WEIGHT GAINS IN SPELLS OF FOUR WEEKS

Age (weeks)	Gains from Birth (lb. oz.)		Four-weekly Gains (oz.)	
	Present Subject	Hammond	Present Subject	Hammond
8	1 11	2 10	—	—
12	3 9	4 8	30	30
16	5 7	6 5	30	29
20	7 11	7 8	36	19
24	8 13	8 11	18	19
28	11 1	10 0	36	21
32	12 9	11 0	24	16
36	13 7	11 12	14	12
40	14 14	12 9	23	13
44	15 12	13 3	14	10
48	16 8	13 9	12	6
52	16 4	14 7	4	14

Teething was rapid towards the end of August and the child failed to gain weight in one week.

Energy Intake. The energy intakes varied greatly from week to week. For some, this was due to illness, but in others there was no obvious cause except that the baby was not eating well. Thus, the daily calorie intake during the week ending June 19 was 699, and it rose to 719, 780, 824 and 893 in the next four weeks. After she had been off her food the energy intakes became greater than before. Thus, after the attack of bronchitis, the daily calorie intake rose to 988, a value higher than ever before. Fig. 1 shows that growth and calorie intakes went hand in hand. When the child was in the care of her father or her aunt the energy intakes were lower than when she was in the care of her mother. The father and aunt were told how to prepare the feeds, but the father gave more sugar and less cereals and the aunt gave less sugar and less cereals. The result was that energy intakes were less.

Table 2a gives the data on growth and energy intakes for the second, third and fourth quarters

TABLE 2A

GROWTH AND CALORIE DATA FOR THE FOUR QUARTERS (13 WEEKS) OF THE YEAR

Quarter	Weight Gain (lb.	oz.)	Weight Gain (Parfit, 1951) (lb.	oz.)	Average Weekly Weight Gain (oz.)	Daily Calorie Intake	Calorie Intake (per lb. body weight)	Holt and Fales (1921) Standard (calories per lb. body weight)
1st	4	2	4	11	5·1	—	—	—
2nd	5	10	4	3	6·9	686	48	51
3rd	4	11	2	14	5·8	803	42	47
4th	1	13	2	6	2·2	841	37	45

TABLE 2B

GROWTH AND CALORIE INTAKES IN THREE PHASES OF GROWTH

Period	No. of Weeks	Weight Gain (oz./week)	Daily Calorie Intake	Calorie Intake (per lb. body weight)	Holt and Fales (1921) Standard (calories per lb. body weight)
Feb. 24-May 19	12	8·2	665	55	53
May 26-July 14	7	9·0	794	46	48
July 14-Nov. 24	19	3·9	819	38	45

(13 weeks) of the child's life. Table 2b gives the same kind of data for the three phases of growth (1), (2), (3) above. Both of these Tables show that total calorie intakes increased, but that calorie intakes per lb. of body weight decreased with increase in age. During the 19 week stretch from the age of 29½ to 48½ weeks, when the gain was about 4 oz. a week, the calorie intake was only 38 per lb. of body weight. Tables 2a and 2b also show the calorie intakes per lb. of body weight based on data given by Holt and Fales (1921). For the early months the actual intakes were much the same as those given by Holt and Fales but in the fourth quarter and the 19 weeks from the age of 29½ to 48½ weeks they were much less than the standards given by Holt and Fales.

The Intake of Nutrients. For the whole time of the study protein intakes were 30-40 g. daily, fat about 30 g., calcium 1-1½ g., iron 1 mg. daily up to about 12 weeks of age rising to 10 mg. at about 16 weeks; vitamin A just over 1,000 i.u. up to the twenty-fourth week, rising to 4,000 i.u.; vitamin B about 300 i.u. until 17 weeks, rising to 600 i.u., and ascorbic acid about 8 mg. up to 20 weeks, rising to about 30 to 40 mg. The intakes of vitamins A and C from the normal diet, that is, without cod-liver oil or orange juice, were about 1,000 to 1,500 i.u. daily of A and about 8 mg. daily of C up to about 23 weeks, rising to about 30 mg. after the twenty-third week.

Comment

The date for this single infant are given simply to show what can be learnt from a study of the diet, growth rate and health record of the same subject over some months. Such data for even a small group of infants would be of much value in showing how these and other factors react and their bearing on the rearing of infants.

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PNEUMOTHORAX AND PULMONARY INTERSTITIAL EMPHYSEMA IN THE NEWBORN

BY

N. E. FRANCE, I. GORDON and F. M. HUMPHRIES
From the Mothers' Hospital (Salvation Army) and the Queen Elizabeth Hospital for Children, London

(RECEIVED FOR PUBLICATION MAY 28, 1952)

With the greatly increased interest in neonatal morbidity in recent years it is now realized that pneumothorax and pulmonary interstitial emphysema in the newborn period, for many years regarded as medical curiosities, are not uncommon. Indeed, Davis and Stevens (1930) demonstrated the presence of pneumothorax radiologically in 1% of 702 consecutive babies and Solis-Cohen and Bruck (1934) in approximately 2% of 500 neonates. While the majority recover spontaneously, in others the condition progresses rapidly and death may ensue.

The following cases illustrate the association between obstructive atelectasis, pulmonary interstitial emphysema and pneumothorax. In addition, two fatal cases of a congenital anomaly of the lungs (pulmonary alveolar dysplasia) are described in both of which pulmonary interstitial emphysema developed. Pulmonary alveolar dysplasia does not appear to have been recorded before as a cause of interstitial emphysema and pneumothorax in the newborn.

Case Reports

Case 1. This girl was the firstborn of a 36-year-old mother and was delivered by forceps as foetal distress developed at the end of the first stage of labour. The baby weighed 2,965 g. (6 lb. 9 oz.) and was severely asphyxiated at birth. She gasped before mucus catheterization was performed. A good deal of meconium-stained fluid was removed from the pharynx, and intranasal oxygen was given. Regular respirations were established in 10 minutes but the baby was pale and moaning. When 30 minutes old she bled from the umbilical cord and became white and shocked. A transfusion of 60 ml. of bank blood (Group O Rh negative) was given via the umbilical vein with considerable improvement in her condition although her vigour was slight. She had periods of restlessness and at 63 hours of age she was still pale and slightly cyanosed with a whining cry. There were then signs of left pneumothorax with hyper-resonance and poor air entry, and bronchial breathing and occasional crepitations were heard over the right lung. A radiograph of the chest confirmed the diagnosis of left pneumothorax and showed gross displacement of the heart to the right (Fig. 1).

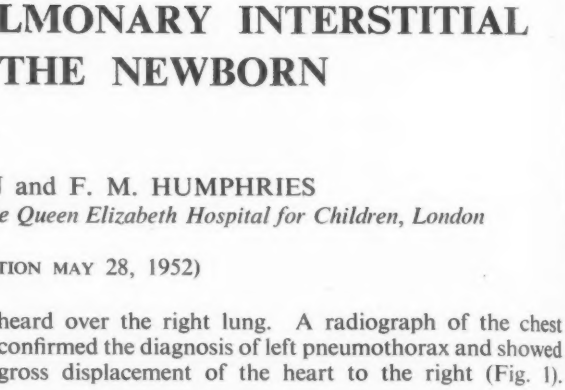

FIG. 1.—Radiograph of Case 1 showing left-sided pneumothorax and displacement of the heart to the right.

Air, 360 ml., was withdrawn from the left pleural sac by a needle. It was not under pressure and its removal produced no alteration in the child's condition. Twelve hours later her condition was critical and, in order to exclude the presence of tension pneumothorax, needles were inserted into both pleural cavities but no air was removed. Some hours later the baby was restless and twitching; she produced several blood-stained vomits and a slightly blood-stained vaginal discharge. A further radiograph showed a pneumothorax, now on the right side with a swing of the heart back to the left. The baby was still pale, and slightly cyanosed with gasping breathing. The haemoglobin was 100% (14·8 g. per 100 ml.). She continued to vomit blood and when 4 days old was given a transfusion of fresh blood. In spite of several cyanotic attacks her condition gradually improved, and a radiograph taken at 9 days showed complete absorption of all air from the pleural sacs and, at 17 days, complete pulmonary expansion. Streptomycin, 25 mg. intramuscularly four-hourly, was given

for the first three days of life and penicillin, 50,000 units intramuscularly four-hourly, for 14 days.

SUMMARY. Intra-uterine asphyxia; aspiration of meconium-stained liquor amnii; obstructive atelectasis; probable pulmonary interstitial emphysema; haemorrhagic disease; bilateral pneumothorax; recovery.

Case 2. A boy weighing 3,680 g. (8 lb. 2 oz.) at birth, born at the Mothers' Hospital, was the third child of a 34-year-old mother. Her previous pregnancies were normal but a prolapsed uterus had necessitated an extensive perineal repair. The child was therefore delivered by caesarean section at 38 weeks of gestation. He was limp at birth and responded slowly to mucus catheterization and intranasal oxygen. A considerable amount of mucus drained from the upper respiratory passages for several hours after birth. When 4 hours old he was vigorous and had a good colour although slight rib recession was noted. No adventitious sounds were heard in the chest and there was good air entry over all areas. On the second day of life he was slightly cyanosed and moaning and showed increased rib recession and diminished air entry over both lung fields. Penicillin, 20,000 units, was given intramuscularly every four hours and the baby was placed in an oxygen bell. The following day he was much worse with deep cyanosis, weakness and rapid, grunting respirations. Numerous inspiratory crepitations were heard over the front of the left chest. Nasal and throat swabs produced a profuse growth of *Streptococcus haemolyticus*. Despite intramuscular injections of streptomycin, 50 mg. eight-hourly, death occurred 48 hours after birth.

A post-mortem radiograph showed partial left-sided pneumothorax with gross displacement of the heart to the right. The right lung showed no obvious aeration but the left lung appeared emphysematous (Fig. 2).

NECROPSY FINDINGS. The body was that of a newborn white male weighing 3,630 g. and measuring 53 cm. in length (crown-heel). When the chest was opened under water a few millilitres of air escaped from the left pleural cavity. The right lung was covered by normal pleura and was generally pink except for the lower lobe posteriorly which was purple and firm. The left lung showed numerous subpleural bullae over both lobes and large numbers of round, air-containing spaces on the cut surface. Most of these bubbles measured about 3 mm. in diameter but others were as large as 6×4 mm. A haemolytic streptococcus (Group A) was isolated from both the throat and bronchus.

Apart from a few small subarachnoid haemorrhages over the cerebrum, all other organs were normal.

MICROSCOPY. In the right lung most of the alveoli were smaller than normal and contained cornified amniotic cells and granular material, frequently associated with a marked inflammatory exudate. Other alveoli were atelectatic.

In addition to the features seen in the right lung there was massive interstitial emphysema in the left lung (Fig. 3). The bubbles of air lay in the connective tissue surrounding the septal blood vessels and extended to the hilum and subpleural tissue. In many places blood vessels were isolated in the centres of air spaces (Fig. 4).

SUMMARY. Aspiration of liquor ammii; obstructive atelectasis; aspiration pneumonia (streptococcal); pulmonary interstitial emphysema; left pneumothorax; death.

Case 3. A boy weighing 2,745 g. (6 lb. 1 oz.) at birth, born at the Mothers' Hospital, was the result of the third

FIG. 3.—Whole lung section (left) of Case 2 showing the distribution of interstitial emphysema in the pulmonary septa.

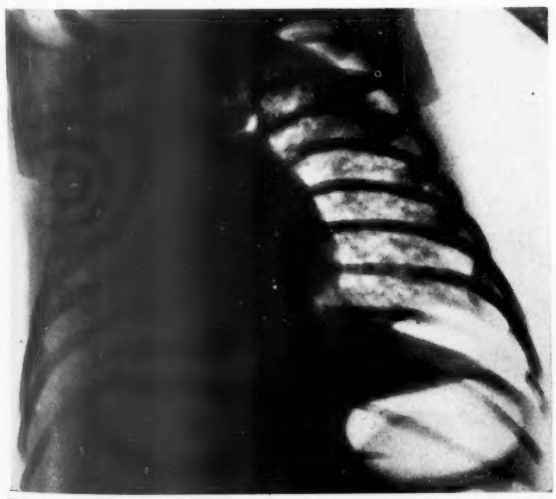

FIG. 2.—Post-mortem radiograph of Case 2 showing left-sided pneumothorax with displacement of the heart to the right, poor aeration of the right lung and emphysema of the left lung.

FIG. 4.—Photomicrograph of lung of Case 2 showing large air spaces in the perivascular tissue (×29).

pregnancy of a 31-year-old mother with a generally contracted pelvis and suffering from mitral stenosis. Delivery was by caesarean section at 38 weeks' gestation. The baby's condition was quite satisfactory at birth and remained so until the age of 3 days when he vomited several times and was jaundiced. By the next day he was very ill with cyanosis, rapid breathing, some subcostal recession and a temperature of 104° F. He was treated with penicillin, 150,000 units daily in divided doses intramuscularly, and with oxygen, and on the following day was much improved. It was noted that the right side of the thorax moved less than the left side and coarse crepitations were heard at the right base. A post-nasal swab produced a pure growth of *B. friedländeri* insensitive to penicillin (20 units per ml.). A radiograph of the thorax showed a right-sided pneumothorax with collapse of all lobes of the lung but no displacement of the heart (Fig. 5). As the child was steadily improving

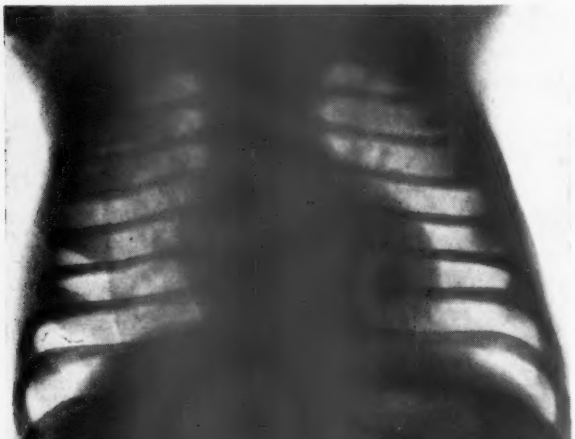

FIG. 5.—Radiograph of Case 3 showing right-sided pneumothorax with no mediastinal displacement.

penicillin therapy was continued for seven days, in spite of the insensitivity of the organism *in vitro*. The child gained weight and on the seventeenth day after birth a radiograph showed normal lung fields with no evidence of pneumothorax.

SUMMARY. Pneumonia (*B. friedländeri*); presumably pulmonary interstitial emphysema; right pneumothorax; recovery.

Case 4. This boy, born at home, was the result of the mother's ninth pregnancy and was born eight weeks prematurely following mild ante-partum haemorrhage. At birth he weighed 2,090 g. (4 lb. 10 oz.) and remained well until 16 days old when, half an hour after a feed, he started to scream and to froth at the mouth. He became grey and collapsed but rapidly recovered. He was admitted to the Queen Elizabeth Hospital for Children. No abnormal physical signs were elicited but a radiograph of the thorax 24 hours later showed bilateral partial pneumothoraces without mediastinal displacement (Fig. 6). No specific treatment was given and at 20 days of age the air had all been absorbed. During the next year he

FIG. 6.—Radiograph of Case 4 at 17 days of age showing bilateral pneumothoraces.

suffered from several mild bronchitic attacks. When 16 months old a radiograph of the chest showed left basal pneumonia which, on resolution, revealed a pneumatocoele in the posterior part of the left lower lobe (Fig. 7).

SUMMARY. Antenatal anoxaemia; presumably aspiration of liquor amnii; possibly pulmonary interstitial emphysema; bilateral pneumothorax at 16 days of age; pneumonia and pneumatocoele at 16 months of age; recovery.

FIG 7.—Radiograph of Case 4 at 16 months of age showing pneumatocoele in the left lower lobe posteriorly.

Case 5. A boy weighing 2,400 g. (5 lb. 5 oz.) at birth was born at the Mothers' Hospital of a primiparous mother aged 22 years. Two attempts at external version were unsuccessful and delivery in the thirty-eighth week of pregnancy was by the breech with extended arms and legs. There was foetal distress and the child was thought to have inspired before the birth of the head. He was limp and cyanosed at birth. When examined he had marked bilateral rib recession

and coarse crepitations were heard over both lung fields. The abdomen was scaphoid. Blood-stained mucus was aspirated from the pharynx. He was given 20,000 units of penicillin intramuscularly but his condition rapidly deteriorated with very marked cyanosis. He died two and a half hours after birth. A post-mortem radiograph of the thorax showed partial right-sided pneumothorax with displacement of the heart to the left (Fig. 8).

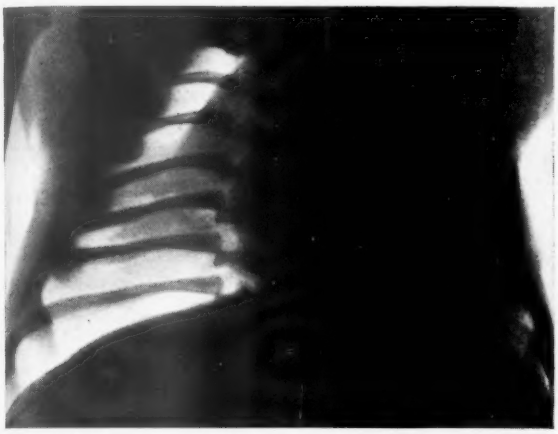

FIG. 8.—Post-mortem radiograph of Case 5 showing right-sided pneumothorax and displacement of the heart to the left.

NECROPSY FINDINGS. The body was that of a white male weighing 2,400 g. and measuring 50 cm. in length (crown-heel). On opening the thorax under water a number of bubbles issued from the right pleural sac. Both lungs were light purple, had a rubbery consistency and showed numerous subpleural air bubbles up to 5 mm. in diameter over all surfaces. A number of small bubbles were present in the septa on the cut surfaces and these extended into the mediastinum.

Both kidneys were tiny, each measuring $2{\cdot}4 \times 1{\cdot}6 \times 1{\cdot}2$ cm., and were composed of numerous small cysts up to 3 mm. in diameter. Both pelves were of normal size but the ureters were grossly dilated. The bladder had an average thickness of 6 mm., the increase being apparently due to thickening of the mucosa which was everywhere firm and rough. There was no evidence of an organic urethral obstruction and the abdominal muscles were normal. The testes lay 4 cm. above the brim of the pelvis.

MICROSCOPY. The lobules of the lung were separated from each other by large spaces in the septa surrounding the blood vessels and representing interstitial emphysema. Although some alveoli were collapsed most were expanded and had a distinctive appearance (Figs. 9 and 10). The alveolar walls were two to three times their normal thickness and were composed largely of loose fibrillary tissue in which cells were few and capillaries almost absent. The alveoli were lined by an incomplete lining of flattened cells with small elongated nuclei. Projecting from the wall into the lumen of each alveolus were three or four small tufts containing one to four capillaries cut in cross section. The capillaries were separated from the alveolar lumen by a thin basement membrane only. The remaining pulmonary elements were not remarkable although bronchioles appeared rather more numerous than usual, suggesting that there was a relative decrease in the amount of parenchymatous tissue.

Both kidneys were composed mainly of fibrous tissue in which were isolated tubules and occasional glomeruli. There were numerous small cysts lined by flattened epithelium and in one area there was a cartilaginous plaque. The ureters were composed of connective and fibrous tissue in which were occasional smooth muscle fibres. The muscle of the bladder was thin and atrophic, the greater part of the wall being composed of dense fibrous tissue in which were small foci of calcification.

SUMMARY. Congenital alveolar dysplasia of lungs; hypoplastic cystic kidneys and mega-ureters; pulmonary interstitial emphysema; right pneumothorax; death.

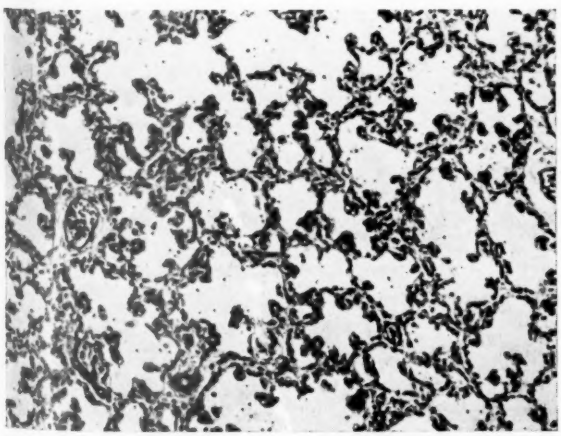

FIG. 9.—Photomicrograph of Case 5 showing the distinctive pattern of the lung in alveolar dysplasia (×90).

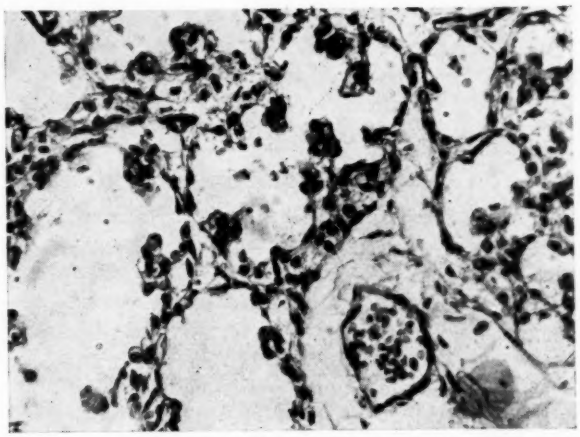

FIG. 10.—Photomicrograph of Case 5 showing the abnormalities of the alveolar walls (×240).

Case 6. A girl, weighing 2,210 g. (4 lb. 14 oz.) at birth, a second child, was born at home in the thirty-seventh week of pregnancy and was delivered by the vertex. There was very little liquor amnii. No evidence of foetal distress was detected but at birth there was white asphyxia. Only a small amount of mucus was obtained on using the mucus catheter. When examined by a doctor 50 minutes after birth she was very limp and pale with feeble, gasping respirations and a slow heart rate. Numerous crepitations were heard anteriorly over both lungs. Her condition rapidly deteriorated and she died in the ambulance on the way to the Mothers' Hospital when one and a half hours old.

On examination after death the abdomen was distended and both kidneys were palpable.

NECROPSY FINDINGS. The body was that of a premature white female weighing 2,210 g. and measuring 46 cm. in length (crown-heel). There was no evidence of pneumothorax but both lungs showed marked interstitial emphysema both in the subpleural tissue and in the septa and extending to some extent into the mediastinum.

Both kidneys were very large, measuring $8 \times 5 \times 4$ cm., and were made up of innumerable tiny cystic spaces containing mucinous fluid. The liver showed patchy fibrosis over the upper surface of the right lobe. Its consistency was firm and the cut surface showed increased fibrous tissue around the larger portal tracts.

MICROSCOPY. The histological picture of the lungs was identical to that of Case 5. The kidneys were composed almost entirely of numerous small cysts lined by a single layer of cuboidal or flattened epithelium. Occasional groups of glomeruli and tubules were present in the interstitial tissue. The liver showed considerable increase in the amount of fibrous tissue around the portal tracts. The bile ducts were numerous, dilated and distorted into bizarre shapes. Many of their lining cells contained granules of haemosiderin.

SUMMARY. Congenital alveolar dysplasia of lungs; polycystic kidneys; cystic fibrosis of liver; pulmonary interstitial emphysema; death.

Discussion

Pathogenesis of Pneumothorax. The causes of pneumothorax in the newborn infant were summarized by DeCosta (1940) as (1) congenital anomalies, (2) pulmonary infection, (3) trauma, (4) mechanical obstruction and (5) artificial respiration.

The first three of these may be illustrated respectively by broncho-pleural fistula (Wiener, 1930), rupture of a pulmonary abscess or pneumatocoele into a pleural sac (Wilkinson, 1936) and direct trauma to the lung by a fractured bone (Riedweg, 1934, Case 7) or exploring needle, all of which mechanisms are readily understood.

Mechanical obstruction causing pneumothorax in neonates is probably always intrinsic, the bronchi being obstructed by mucus, vernix caseosa, meconium or viscid inflammatory exudate. Extrinsic obstruction such as may be caused by the umbilical cord around the neck (Salmon, Forbes and Davenport, 1947) is probably important only in that it may produce asphyxia with resultant inhalation of amniotic fluid. Obstruction produces patchy over-distension of alveoli by hyperventilation if respiratory efforts are vigorous or as a compensation to areas of collapse. Similarly alveolar distension may be compensatory to pneumonic consolidation or may be produced by artificial respiration involving the introduction of oxygen under positive pressure into the trachea. Mouth-to-mouth breathing is especially dangerous (Emmert, 1930). It is improbable that over-distension of alveoli can result from normal respiratory movements as was suggested by Strain and Connell (1950) or that intracranial haemorrhage or congenital heart disease (Salmon and Forbes, 1943) are causal factors in alveolar over-distension.

Macklin and Macklin (1944) have demonstrated experimentally that when over-distension of alveoli occurs those alveoli adjacent to blood vessels may rupture and air will then pass into the perivascular connective tissue. Such rupture does not occur when alveoli are completely surrounded by other alveoli or when they lie next to bronchioles, as in such a situation all air-containing passages expand equally and no undue strain is thrown upon the alveolar walls. Once air has escaped into the interstitial tissue it tracks along the vascular sheaths to the hilum and thence into the mediastinum.

Pulmonary interstitial emphysema has important effects on the lung as it tends to splint the lung in a state of inflation and by its perivascular location it interferes with the pulmonary circulation (Macklin and Macklin, 1944). It may cause pulmonary haemorrhage (Salmon, 1947), may assist in the spread of infection (Macklin, 1939) or may rupture into the pleural sac to produce a pneumothorax. Macklin and Macklin (1944) believe that the majority of cases of pneumothorax are produced by the passage of air from the mediastinum into the pleural cavity. Mediastinal emphysema secondary to pulmonary interstitial emphysema produces serious effects by the pressure of air on the heart and great vessels, and they state that when air escapes into the pleural sac, the retroperitoneal tissue or the subcutaneous tissue of the neck it is attended by a relief of symptoms.

Diagnosis of Interstitial Emphysema. The clinical features in cases of established pulmonary interstitial emphysema alone do not appear to have been described although its anatomical features indicate that it may reproduce a similar picture to that of mediastinal emphysema (Salmon, 1947). When the

latter is present there is dyspnoea and cyanosis with hyperexpansion of the chest, shallow, rapid respirations and inspiratory recession. The physical signs of mediastinal emphysema include reduction of the area of cardiac dullness and weakened heart sounds, the result of displacement of the heart from the anterior chest wall (Biering, 1941). The characteristic crepitations heard during systole, which are a feature of the condition in adults, are not detected in the neonatal period (Hamman, 1939). A postero-anterior radiograph of the chest in mediastinal emphysema may show globules of air just outside the lateral margins of the superior mediastinum, whereas the lateral view shows pools of encapsulated air just beneath the sternum (Gumbiner and Cutler, 1941). Pressure effects may produce radiological evidence of pulmonary congestion. The diagnosis of mediastinal emphysema is assured if subcutaneous emphysema of the neck and upper thorax appears, although this is rare in infancy (McMann and Purcell, 1939).

Clinical Diagnosis of Pneumothorax. Pneumothorax in the newborn presents very different pictures. A small pneumothorax may be found, almost by chance, in a radiograph of a baby who looks quite well, or may occur without much alteration of the picture or physical signs in a baby already acutely ill with respiratory distress. A large pneumothorax is likely to cause severe symptoms and may give striking physical signs although the baby may be so acutely ill that physical examination has to be cut to a minimum. Moreover, even striking physical signs when found may not finally establish a diagnosis without x-ray examination. A bilateral pneumothorax (Case 4) or a pneumothorax associated with pneumonia and causing no displacement of the heart (Case 3) may make the interpretation of signs difficult.

Clinical diagnosis in the neonatal period is notoriously difficult; this is in part due to the fact that essentially similar clinical pictures can be produced by very different pathological conditions as indicated below. In the case of lung conditions there is difficulty in interpreting the significance of the signs elicited in the tiny chest; for example, if there is a difference in resonance to percussion between the two sides, it may not be easy to decide which is abnormal, especially as minor displacements of the heart are difficult to detect with certainty without the help of radiographs. Pneumothorax and diaphragmatic hernia can cause similar signs in the neonatal period. Dyspnoea, cyanosis, perhaps exaggerated respiratory efforts, displacement of the heart, weak or absent breath sounds and diminished movements on the affected side of the chest and even hyper-resonance on this side may be present in both conditions. It is obviously essential to be sure of the correct diagnosis before a needle puncture is made for a supposed pneumothorax. In the differential diagnosis of pneumothorax other conditions to be considered are compensatory over-distension of one lung on account of partial agenesis or failure of expansion of the other lung, and possibly an air-containing pulmonary cyst. Pneumonia, eventration of the diaphragm or a phrenic nerve paralysis can cause respiratory distress, exaggerated respiratory efforts and a difference in percussion note between the two sides of the lower chest, in these cases the less resonant side being the abnormal one.

If some of the pitfalls of diagnosis are borne in mind and one considers the history of the case as well as the physical signs, a clinical diagnosis can be made with some certainty in a proportion of cases of pneumothorax; in others only a radiograph will establish its presence. However, it is the large pneumothorax causing severe symptoms in which the establishment of the diagnosis is urgent and in such cases the history may be of material help.

The Relationship between Obstructive Atelectasis and Pneumothorax. In the history of a pneumothorax the antecedent factors are often intrauterine asphyxia, aspiration of amniotic sac contents and obstructive atelectasis with or without pneumonia.

Five cases of pneumothorax have been described, and of these, three (Cases 1, 2 and 4) followed inhalation of fluid before or at birth with consequent obstructive atelectasis, one (Case 3) followed infection with Friedländer's bacillus, possibly causing obstruction of the bronchi with viscid secretion as well as damage to tissues from infection, and one (Case 5) resulted from a congenital anomaly of the alveoli preventing adequate oxygenation of the blood as well as preventing normal expansion of the lungs in response to respiratory efforts. Pulmonary interstitial emphysema is likely to arise when there is patchy obstruction to the entrance of air into the alveoli of an infant who has the vigour to make respiratory efforts of sufficient strength to over-distend and cause the rupture of alveoli; an infant whose respiratory efforts are feeble throughout is not likely to burst alveoli. If we exclude methods of resuscitation probably the commonest cause of pneumothorax in the newborn is inhalation of amniotic sac contents with obstructive atelectasis, interstitial emphysema and the rupture of bullae. Thus, when faced with a possible case of pneumothorax in the newborn, one should inquire into

factors likely to have produced intra-uterine asphyxia, such as partial separation of the placenta as indicated by ante-partum haemorrhage (Case 4), continuing compression of the placenta by severe and frequent pains or interruption of the foetal circulation by a prolapsed cord; evidence of foetal asphyxia *in utero* in the shape of change in the foetal pulse rate or the passage of meconium (Case 1); evidence of asphyxia at birth (Cases 1, 2 and 5); signs of obstructive atelectasis with fairly vigorous respiratory efforts and subcostal recession at each inspiration.

White asphyxia, slow establishment of respiration with continuing pallor, cyanosis or cyanotic attacks, shallow, irregular respirations, twitching and restlessness or complete lethargy may betoken intracranial trauma with haemorrhage or may result from asphyxia alone. In either case there will often be obstructive atelectasis, though if breathing is feeble this usually gives no distinctive physical signs and is unlikely to cause interstitial emphysema or pneumothorax. If after birth the baby has sufficient vigour to make good respiratory efforts producing marked subcostal recession, that is the infant who may develop interstitial emphysema and pneumothorax, though with failing vigour the respirations may become shallow again and recessions cease to be present.

The infant (Case 3) who developed a pneumothorax with pneumonia presumably developed interstitial emphysema from similar patchy obstruction of smaller bronchi as that leading to interstitial emphysema in obstructive atelectasis. The relationship between the pneumothorax and the subsequently found pneumatocoele in Case 4 is difficult to assess. Bilateral pneumothoraces, as in this case, are not likely to be produced by rupture of congenital cysts although this has been described by Miller (1926). The process resulting in the rupture of aveoli into the pleural sacs may have produced an encapsulated collection of air in the pulmonary supporting tissue. It is more probable, however, that the pneumatocoele arose independently of the pneumothorax and secondary to an inflammatory process occurring at 16 months of age.

Alveolar Dysplasia and Pneumothorax. Although Case 6 showed no pneumothorax, it is included in the series because the pathology was identical to that of Case 5. Both of these children showed an unusual alveolar pattern which may be described as alveolar dysplasia of a type distinct from that described by MacMahon (1948).

MacMahon's alveolar dysplasia is characterized by the presence of small alveoli separated by thick alveolar walls resembling foetal mesenchyme with an alveolar lining similar to that of mature lung (MacMahon, 1948). His findings have also been described by Kaufman and Spiro (1951) although many pathologists are doubtful of its existence as a pathological entity (Blystad, Landing and Smith, 1951).

The abnormal lungs in the present cases were associated with congenitally cystic kidneys and in one case with cystic changes in the liver. They presented the following pathological features: (1) Although only a few hours old the alveoli were all expanded to about normal size. (2) The total amount of alveolar tissue was small in proportion to the amount of supporting tissue. (3) The alveolar walls were two to three times their normal thickness and were relatively acellular and avascular. (4) The alveoli were incompletely lined by a single layer of flattened endothelial cells. (5) Projecting into the lumen of each alveolus were small tufts of capillaries with no endothelial covering.

It is probable that lungs so affected are incapable of expansion to the size demanded by the bony and muscular development of the thoracic cage with the result that over-distension and rupture of alveoli occur.

The association of hypoplasia of the lungs and bilateral renal agenesis was first described by Potter (1946) who noted also that with renal agenesis deficiency of liquor amnii (compare Case 6) had been recorded. She described the histological picture as showing inadequate parenchymatous development with rudimentary alveoli often lined by cuboidal epithelium and inhibition of capillary ingrowth into the alveolar walls. The lungs thus resembled those of a foetus of a lower gestational age than the one in which they were found. This observation has been confirmed by Leffler (1951) whose photomicrographs show atelectatic, immature lung. However, the possibility remains that if such alveoli were expanded, they would show a similar picture to that seen in the present cases. Potter (1952) states that she observed moderate hypoplasia of the lungs associated with polycystic kidneys. Histologically they resembled the hypoplastic lungs found in cases of renal agenesis. No other reference to pulmonary changes in any way similar to those described in Cases 5 and 6 has been found in the literature.

Summary

Five cases of pneumothorax and one case of pulmonary interstitial emphysema in the newborn period are described.

The pathogenesis of pulmonary interstitial

emphysema and its relationship to obstructive atelectasis and pneumothorax are discussed.

The clinical and radiological features of pneumothorax in neonates are discussed.

The pathological features of an unusual type of alveolar dysplasia are described.

We are indebted to Dr. H. M. Mackay for permission to publish Cases 1, 2, 3, 5 and 6, and for her great help and encouragement. We also wish to thank Dr. N. Jacoby for permission to publish Case 4, Dr. C. J. Hodson for his advice on the radiographs, and Dr. B. Levin for his criticism. Cases 2, 5 and 6 form part of an investigation of foetal and neonatal death supported by a British Medical Association Research Scholarship held by one of us (N.E.F.)

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AN UNUSUAL CASE OF NEONATAL URAEMIA

BY

W. A. B. CAMPBELL and JOAN S. DALES

From the Royal Belfast Hospital for Sick Children

(RECEIVED FOR PUBLICATION MAY 27, 1952)

Uraemia, generally extra-renal in origin, is not uncommon in infancy, but comparatively few cases occur in the neonatal period. The following case of extreme uraemia occurring in an infant dying on the eighth day of life is of interest not only on account of the early manifestation of the uraemia, but on account of its degree and the difficulty which has been experienced in establishing the cause.

Case Report

J.B., a boy, was born at home on October 18, 1951, and admitted to the county hospital on October 20 with a history of vomiting and cyanotic attacks, the latter made worse by swallowing. The confinement was apparently normal but no details are, unfortunately, available. Birth weight was ' about 6 lb. '. The infant did not improve in the county hospital and on October 22 was transferred to the Royal Belfast Hospital for Sick Children with a tentative diagnosis of congenital heart disease and possibly some oesophageal anomaly as well.

On admission, the general appearance of the infant aroused immediate comment. He lay in the cot, immobile, with the limbs flexed at the knees, hips and elbows (Fig. 1); only a few degrees of movement were possible at any of these joints. The face was smooth with little expression, and rather resembled that of an old man. The eyes were widely set with small epicanthic folds, the nose large and hooked with gaping nostrils, and the ears large and flabby, set low in the head (Figs. 2 and 3). The chest was barrel-shaped with poor excursion, and a definite increase in the antero-posterior diameter. The skin of the limbs, and to a lesser extent of the trunk, was thickened, could not be lifted in the fingers, and gave the limbs a curious feel as of ' cold chicken '.

FIG. 1.—J. B. showing flexion deformity of limbs.

FIGS. 2 and 3.—J. B. showing facies.

The child's general condition on admission was poor with cyanosis and respiratory distress and slight depression of the fontanelle. There were crepitations in both lungs, most marked at the left base. The heart sounds were very faint, but appeared to be otherwise normal with no murmur. No abnormality was detected in the abdomen, which was soft.

In view of the history of vomiting and cyanosis, the infant was examined under the x-ray screen; a catheter passed into the oesophagus entered the stomach with ease, and when a small amount of lipiodol was allowed to flow into the oesophagus, none passed into the lung fields, thus ruling out any anomaly of the oesophagus. There was no evidence of consolidation or of atelectasis in the lung fields. The upper dorsal vertebrae were more clearly seen than in the average case, and the possibility of an abnormality of the great vessels was considered.

The rectal temperature on admission was 96° F. and the clinical picture that of sclerema. The facies, however, also suggested the possibility of some congenital abnormality of the kidneys, since the infant bore a marked resemblance to those cases of renal agenesis described by Potter (1946).

The child was placed in an oxygen tent and warmed

gently. A slow intravenous infusion of half-strength Hartmann's solution in 5% dextrose was started, and allowed to run at the rate of 400 ml. per day. In addition he was given a 1 oz. feed three-hourly, containing ' ideal milk ', 2 drachms, water, 6 drachms, and ½ drachm glucose; he took the feed with difficulty. Streptomycin and penicillin were given by injection as a precaution against infection.

He had frequent cyanotic attacks despite the oxygen and vomited darkish brown material occasionally. The bowels moved twice or three times daily, the stools being dark and semi-formed. It was noted that even when hydration appeared adequately restored he passed very little urine, and a measured 24-hour specimen consisted of 1 oz. only.

Investigations bearing on renal function are shown in Table 1.

TABLE 1

SERUM AND URINARY FINDINGS BEARING ON RENAL FUNCTION

		October 25, 1951	October 26, 1951
Blood urea (mg. per 100 ml.)		900	782
Serum chloride	(mg. per 100 ml.)	359	318
	(m.Eq.)	103	91
Sodium	(mg. per 100 ml.)	—*	341
	(m.Eq.)	—	148
Potassium	(mg. per 100 ml.)	16·3	22·7
	(m.Eq.)	4·2	5·8
Urinary chloride	(mg. per 100 ml.)	—	78
Urea + ammonia	(mg. per 100 ml.)	—	1,040
Urine/plasma ratio: Chloride		—	0·24
Urea		—	1·3
Serum Albumin	(g. per 100 ml.)	4·6	—
Protein	(g. per 100 ml.)	—	6·5
Urinary protein	(mg. per 100 ml.)	—	60

* — = not estimated. Urinary estimations made on 24-hour specimen (30 ml.).

The child's condition became progressively worse and the cyanotic attacks more frequent, and he died on the evening of October 26 at the age of 8 days.

The clinical diagnosis was uraemia probably due to some congenital abnormality of the kidneys, sclerema, and possibly a congenital cardiac defect.

Necropsy Report

A necropsy was carried out on the following morning, October 27, by Dr. D. G. F. Harriman.

There was no excess fluid in any of the body cavities. There was no congenital abnormality in the heart and the origins of the great vessels and of the coronary arteries were normal. Both lungs were oedematous and congested, with small areas of consolidation suggestive of atelectasis. The liver, spleen, pancreas and alimentary tract appeared entirely normal. Both kidneys were structurally normal, with foetal lobulation; the cortex and medulla were distinct and of normal width. The pelvis and ureter on both sides were normal, not dilated, and communicated with the bladder. The bladder contained no urine and was not dilated.

Histology. A histological examination gave the following information.

In the heart there was moderate glycogen vacuolation of muscle; there were no changes suggestive of elastosis.

Massive oedema and haemorrhage were seen in all sections of the lungs, but no signs of pneumonia. Some bronchioles contained extremely eosinophilic material (fibrin) without any surrounding inflammation.

In the liver mid-zonal vacuolation of many cells was seen.

A small number of acini of the pancreas were dilated with flattened cells and inspissated material in the lumen.

The neonatal zone of the suprarenal was small, showing early necrosis.

Sections taken from several regions in both kidneys revealed a normally formed cortex. Nephrogenesis was complete and no glomeruli could be found showing any degree of sclerosis. There was general vascular congestion, and some blood was present in collecting tubules without any epithelial reaction. Occasional vacuolation of tubular lining cells was present. The pelvis showed no inflammatory change.

The thymus showed early atrophy, with an increase in Hassal's corpuscles and gross depletion of lymphocytes in the cortex.

The epithelium was normal. It was unfortunately impossible to take a section from the areas showing clinical sclerema.

Discussion

From the findings at necropsy it is obvious that the clinical diagnosis was false, both insofar as there was no anatomical abnormality of the urinary tract, and that the heart also was normal.

Two possible causes of the extreme azotaemia remain; either the whole picture is one of extra-renal azotaemia developing in extra-uterine life, or there was in fact a functional abnormality of the kidneys not accompanied by any histological changes.

The facies of this infant so closely resembled that described by Potter (1946) and others in renal agenesis and renal hypoplasia, that it is tempting to consider the theory that this infant had gross functional renal failure of foetal origin. If the infant had been born with a normal blood urea level it is difficult to explain how, even with complete failure of all renal excretion, the blood urea could have risen to such an extent in the course of eight days. If no urine had been formed all the urea produced in the eight days of life must have accumulated in the body fluids. (In the present case there was actually a slight urinary secretion.) From the data of Barlow and McCance (1948) on the excretion of urea in the normal neonate, it can be calculated that in the first eight days of life approximately 510 mg./kg. of body weight of urea would have been

retained. If this had been evenly distributed in the body fluids, which represent about 70% of the body weight of the full term newborn infant (Widdowson and Spray, 1951), it would have represented a rise of about 73 mg. per 100 ml. body water, and a rise in blood urea concentration of 58 mg. per 100 ml. blood. This, if added to the maximum blood urea level found by McCance and Widdowson (1947) on the eighth day of life in infants with normal kidneys, i.e. 25 mg. per 100 ml., would give an approximate level of 80-85 mg. urea per 100 ml. blood, which is very considerably lower than that found in the present case.

It is generally accepted that urea excretion in the foetus is by the placenta, and that the survival of the foetus to full term with complete absence of any kidney tissue is thus made possible. Considerable experimental proof of this placental function has been summarized by Needham (1931) and further evidence was provided by Naeslund (1931). Unfortunately no pathological examination of the placenta of this case was possible.

These workers were dealing with normal infants born of normal mothers, and it is at least theoretically possible that if there is interference with kidney function in either mother or foetus, the latter might be born with a raised blood urea level. Because of the resemblance of our case, in outward appearance at least, to those of bilateral renal agenesis, a search was made in the literature for any record of the blood urea levels of infants born with this abnormality. Although there are now a large number of such cases on record, estimated by Leffler (1951) to reach a total of 163, we have been quite unable to find any in which the blood urea level was estimated. This is largely because most of the cases were diagnosed at necropsy, but even in cases living for a few hours or days no estimation of blood urea levels seems to have been made. Potter (1952) states that post-mortem estimation of blood urea levels showed only moderate elevation, but none of the infants had lived longer than 11 hours.

Unfortunately, as already stated, we have been unable to obtain any information about the mother's health in pregnancy in this case, but it is unlikely that she can have had any severe degree of renal failure. Schofield (1950) compared a group of infants born of toxaemic mothers with a similar group of non-toxaemic mothers, and found a consistently higher level in the toxaemic group but the highest actual level was 119 mg.% (Bevis, 1952).

It is impossible, therefore, to eliminate an intrinsic functional disturbance of tubules and glomeruli as the cause of uraemia in this infant, but equally impossible to state definitely that such a disturbance did in fact exist.

Extra-renal azotaemia is not uncommon in infants and young children from a variety of causes. The commonest cause is dehydration resulting from severe diarrhoea or vomiting or both. Uraemia results in these infants from a combination of haemodynamic factors (reduction in blood volume, increase in colloid osmotic pressure) and general dehydration as a result of which there is insufficient water available for urine formation. Doxiadis (1948) studied 47 infants with blood urea levels between 50 and 500 mg.%, the azotaemia resulting from a variety of dehydrating illnesses, and discusses the mechanisms involved. Both he and Bell (1946) emphasize that if oliguria or anuria persist a stage is reached where the renal function is irreversibly affected, and even the restoration of adequate hydration will not produce a return to normal function. This may occur without any histological evidence of tubular damage.

In our case there was no diarrhoea and the vomiting was never severe, nor was the degree of dehydration on admission more than moderate.

Renal function is also controlled both by the posterior lobe of the pituitary and the adrenal cortex. It is doubtful whether either influence could produce such azotaemia in so short a time, but it is of interest to note that the serum chloride level fell and the serum potassium level rose in the 24-hour interval between the taking of the first and second specimens, which might be indicative of failure of adrenal cortical function. It would be unwise however to lay too much stress on these results alone, and in any event adrenal failure might well be secondary to the general metabolic disturbance.

There remains the possible effect of sclerema on renal function. We have been unable to find any record of the blood urea levels in cases of sclerema. Hughes and Hammond (1948) review the literature on this condition extensively and come to the conclusion that the hardening of fat in the subcutaneous tissues results from severe impairment of the peripheral circulation and shock. Dehydration may be partly masked by the induration of the skin. It seems quite possible that at least some degree of renal failure may result from this peripheral circulatory failure. It was unfortunate that, in our case, the limited necropsy made it impossible to obtain a specimen of the clinically scleremato us skin, but there was little doubt of the existence of the condition.

Summary

A case is described of a newborn infant dying on the eighth day of life in extreme uraemia, with widespread sclerema neonatorum and abnormal facies. There was no demonstrable abnormality in the kidneys at necropsy.

The possible aetiology of the azotaemia is discussed.

We are indebted to Professor F. M. B. Allen and many of our colleagues at the Royal Belfast Hospital for Sick Children for much helpful discussion, to Professor R. A. McCance for his interest and advice, and to Dr. D. G. F. Harriman, Department of Pathology, Queen's University, Belfast, for the pathological report. The photographs were taken by Mr. D. Mehaffey.

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SEXUAL PRECOCITY IN A BOY AFTER MEASLES ENCEPHALOMYELITIS

BY

JOHN APLEY

From the Bristol Royal Hospital for Sick Children

(RECEIVED FOR PUBLICATION MAY 26, 1952)

The clinical impression that measles encephalomyelitis is becoming increasingly prevalent is confirmed by recent studies (Jacobsson and Holmgren, 1949). It is all the more necessary, therefore, to be alert to the sequelae of this baffling condition, sequelae whose rarity is probably exaggerated because of unfamiliarity with their mode of presentation. Thus, in the case to be described of a boy with sexual precocity, which seems quite clearly in retrospect to have been due to measles encephalomyelitis, the only diagnoses which were first considered were those of endocrine tumours.

Probably not more than one child out of 10 dies in the acute stages of measles encephalomyelitis; unfortunately, of those who survive more than half show definite evidence of permanent damage to the central nervous system (Ford, 1944). The commoner residual defects include spastic paralysis, cerebellar ataxy, mental deficiency, personality changes and epilepsy. Among the rarest to have been described is sexual precocity. This interesting sequal is mentioned in all surveys of the subject, though detailed original accounts are hard to discover. Three have been found (Boenheim, 1927, one case; Ford and Guild, 1937, two cases) all referring to girls whose ages (7, 9 and 10 years respectively) bring them rather close to the lower limits of normal puberty. The present report concerns a boy in whom sexual precocity developed soon after the age of 2 years. No other case has apparently been reported in a boy, nor has any case in either sex been described in this country.

Case Report

The patient is the second son in an apparently healthy family. He is said to have been normal at birth (birth weight 6 lb. 3 oz.) after an uncomplicated pregnancy. Development during the first two years of life was uneventful, and there was no delay in passing any of the usual milestones.

At the age of 2 years he had measles, but was ill for no less than 10 weeks. He was, according to the mother, ' sleepy all the time, and it was too much trouble to look at anything or do anything '. During this illness he was incontinent of urine and faeces, though previously these had been controlled. At night ' he slept on his hands and knees, and kept banging his head '.

After the illness he seemed, the mother says, ' different '. During the next year it was noticed that the genitalia were enlarging. He developed violent screaming attacks, which seemed gradually to be replaced by epileptiform seizures; for these he has since been treated medically. He grew rapidly in height and weight, and Fig. 1 shows his precocious general and genital development at the age of 4 years.

At 6 years he was unusually hairy and began to suffer from widespread acne vulgaris. A radiograph of the skull at this time showed no abnormality. At 7 years his voice ' broke '. He began to shave at 11 years, but, according to his mother, should have done so several years earlier.

He continued to grow rapidly, and at 8 years was taller than his brother who is 4 years older; growth in height has slowed down almost completely since the age of 12, and the brother is now much taller than the patient. Some figures of height and weight are fortunately available from school records. They show the patient at 5 years to have been 52½ in. in height and 85 lb. in weight, figures which would be expected at twice his age. At 10¾ years he weighed 118 lb. and was 59½ in. tall. In the subsequent two years he has gained 15 lb. in weight but only ½ in. in height.

At the age of 12 years he was referred for an opinion because of uncontrollable ' giggling attacks ', which had been coming on for some years. They occurred

FIG. 1.—Patient at 4 years, to show marked precocity of general and genital development.

at school, especially during prayers, and he tended to yawn afterwards and to feel rather tired. Very occasionally typical major epileptic manifestations had occurred despite continued treatment with anticonvulsants.

Physical Examination. He was at 12 years of age a big, plump, rather simple lad, with red cheeks and a frequent smile (Fig. 2). The skin was hairy and greasy, with active acne vulgaris on the face and trunk, and many scars of old acneiform eruptions. Striae atrophicae were present on the flanks and lower abdomen. The blood pressure was 110/80 mm. Hg. A functional systolic cardiac murmur was audible. The optic fundi and visual fields appeared normal. No abnormalities were found in the central nervous system or other systems.

FIG. 2.—Patient at 12 years.

Mental and Psychological State. Though the patient considered his ability to be average at school, this opinion was not shared by his schoolmaster who considered him rather backward. His I.Q. was unexpectedly low at 51. It had been assessed at 80 when he was 5 years old, and again at 10 years, though at 11 and 12 years of age it was estimated at 56.

There was no history of sexual activity; he is not particularly attracted to girls, and prefers the company of adults to children of his own age. His ideas as to vocation are variable, and at present he wishes to become either an actor or a B.B.C. announcer.

Investigations at the Age of 12 Years. Blood counts and blood sugar levels were normal. Routine urine examination revealed no abnormalities; the estimation of 17-ketosteroids (calculated as androsterone) gave a figure of 5·6 mg. in 24 hours, which is within the normal range. A radiograph of the skull was normal, but radiographs of long bones showed a moderate degree of chronological advancement. An electroencephalogram showed a pathological tracing, with a wave form reminiscent of the wave-and-spike discharge of petit mal and a moderate potential theta discharge.

Comment

The description of the acute illness, particularly the features of protracted somnolence and loss of sphincter control, leaves little room for doubt, even in retrospect, that this was a case of measles encephalomyelitis. The abrupt changes in developmental pattern, which had previously appeared normal, date back to the time of the illness; to this unfortunate episode the mental retardation, cerebral dysrrhythmia and sexual precocity must therefore be attributed.

The diagnosis in cases of sexual precocity is frequently tinged with out-dated ideas, and the consequent and often unnecessary tumour-hunt may do considerable harm. Jolly's (1951) recent survey synthesizes and simplifies the available information, and is a delightful diagnostic guide. The present case has no exact counterpart among Jolly's 66 cases, but clearly falls into his cerebral group with ' true puberty '. The single feature of enlarged testicles, with the clear-cut history, provides all the data necessary for a complete diagnosis.

I am indebted to Dr. F. L. Golla for information regarding the early history and for the first photograph, to Dr. A. Guirdham for helpful advice concerning the mental and psychological development, and to Dr. B. A. Astley Weston for providing details from the patient's school records.

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Vascular Abnormalities Associated with Pseudoxanthoma Elasticum

H. H. Wolff, J. F. Stokes and B. E. Schlesinger write as follows:

In our article (*Archives of Disease in Childhood*, **27**, 82) we included an electron microphotograph of a skin biopsy taken from a patient with pseudoxanthoma elasticum. In the legend to this photograph and in the text the fibres shown on electron microscopy were referred to as elastic fibres. These fibres should have been described as normal collagen fibres. No elastic fibres could be detected on electron microscopy of the material removed at biopsy. Similar discrepancies between the appearances obtained on light and electron microscopy have also been described in other cases of the same disorder (Tunbridge, *et al.*, 1952) in which elastic fibres were seen under the light microscope but not on examination by electron microscopy.

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BOOK REVIEWS

The Child in Health and Disease. By C. R. GRULEE and R. C. ELEY. 2nd edit. London: Baillière, Tindall & Cox. 1952. Pp. 1255, 304 figures. Price £5 14*s*.

The editors of this text-book comment in their preface that ' medicine is moving so rapidly that print is scarcely dry before there is something new on the subject '. Anyone who has himself contributed to a book in recent years will endorse this statement, as he sees what he thought was reasonably up-to-date becoming outmoded before it appears.

The present edition of Grulee and Eley has been expanded to cover such subjects as adoption and medical supervision of summer camps. The result is a book weighing 6 lb. 1 oz., containing contributions by 87 authors, and retailing at £5 14*s*.

One has the feeling, rightly or wrongly, that each author has been allocated a limited space in which to present his subject, and the result is that while something of everything known to paediatrics is included, and a great deal else besides, few subjects are considered exhaustively, while some indeed are presented almost as thumb-nail sketches. With so many authors, it is inevitable that not all the contributions reach the same standard, and while some sections are quite up-to-the-minute, others appear to have been written relatively too long ago to include the latest work on the subject.

The book is well produced and the figures are mostly clear and informative. Its weight, however, is such that the reviewer was glad to put it down.

Advances in Pediatrics. Vol. 5. Published by The Year Book Publishers, Inc., Chicago. Distributed in the United Kingdom by Inter-Science Publishers, Ltd. 1952. Pp. 273, illustrated. Price £2 16*s*.; U.S.A. $7.00.

The fifth number of this well-known series is as welcome as its forerunners. It contains six authoritative articles by leaders in their respective fields, three from the United States and three from Europe. The need for this kind of book is clearly shown by the fact that it includes an article on vitamin K in haemorrhagic disease of the newborn, a subject already dealt with in Volume 1, while Dr. Hattie Alexander brings her review of the treatment of purulent meningitis, which appeared in Volume 2, up to date in the present publication. There are articles on angiocardiography, iron metabolism and the nephrotic syndrome in children, while Wallgren contributes an objective summary of the present position of B.C.G. vaccination.

The book is well produced and edited, but for its high price one would have expected to find a better quality of paper.

Management of the Newborn. By ARTHUR HAWLEY PARMELEE. Chicago, U.S.A.: The Year Book Publishers. Distributed in Great Britain by Interscience Publishers Limited, 1952. Pp. 358, illustrated. Price £2 14*s*. ; U.S.A. $7.00.

One of the drawbacks of the march of science is that it is becoming increasingly difficult to present the newer knowledge in an attractive manner or in one which is easy to read. Professor Parmelee's book is an exception in that it is attractively laid out and essentially readable. It makes no attempt to scale the scientific heights, nor does it essay much critical appraisal of controversial matters on most of which the author has a suitably open mind. Yet running through the book is a rich vein of what is obviously first-hand knowledge and experience, and in many sections one feels that here is the art of medicine at its best, to be read with profit by all those who deal with patients as well as cases.

Scholarships in Aid of Scientific Research

The Council of the British Medical Association is prepared to receive applications for research scholarships, as follows:

An Ernest Hart Memorial Scholarship of the value of £250

A Walter Dixon Scholarship of the value of £250

One or More Research Scholarships each of the value of £200

These scholarships are given to candidates whom the Science Committee of the Association recommends as qualified to undertake research in any subject (including State medicine) relating to the causation, prevention, or treatment of disease.

Each scholarship is tenable for one year, beginning on October 1, 1953. A scholar may be re-appointed for not more than two additional terms. A scholar is not necessarily required to devote the whole of his or her time to the work of research, but may be a member of H.M. Forces or may hold a junior appointment at a university, medical school or hospital, provided the duties of such appointment will not, in the opinion of the Science Committee, interfere with his or her work as a scholar.

Applications for scholarships must be made not later than March 31, 1953, on the prescribed form, a copy of which will be supplied by the Secretary on application.

Applicants are required to furnish the names of three referees who are competent to speak as to their capacity for the research contemplated.

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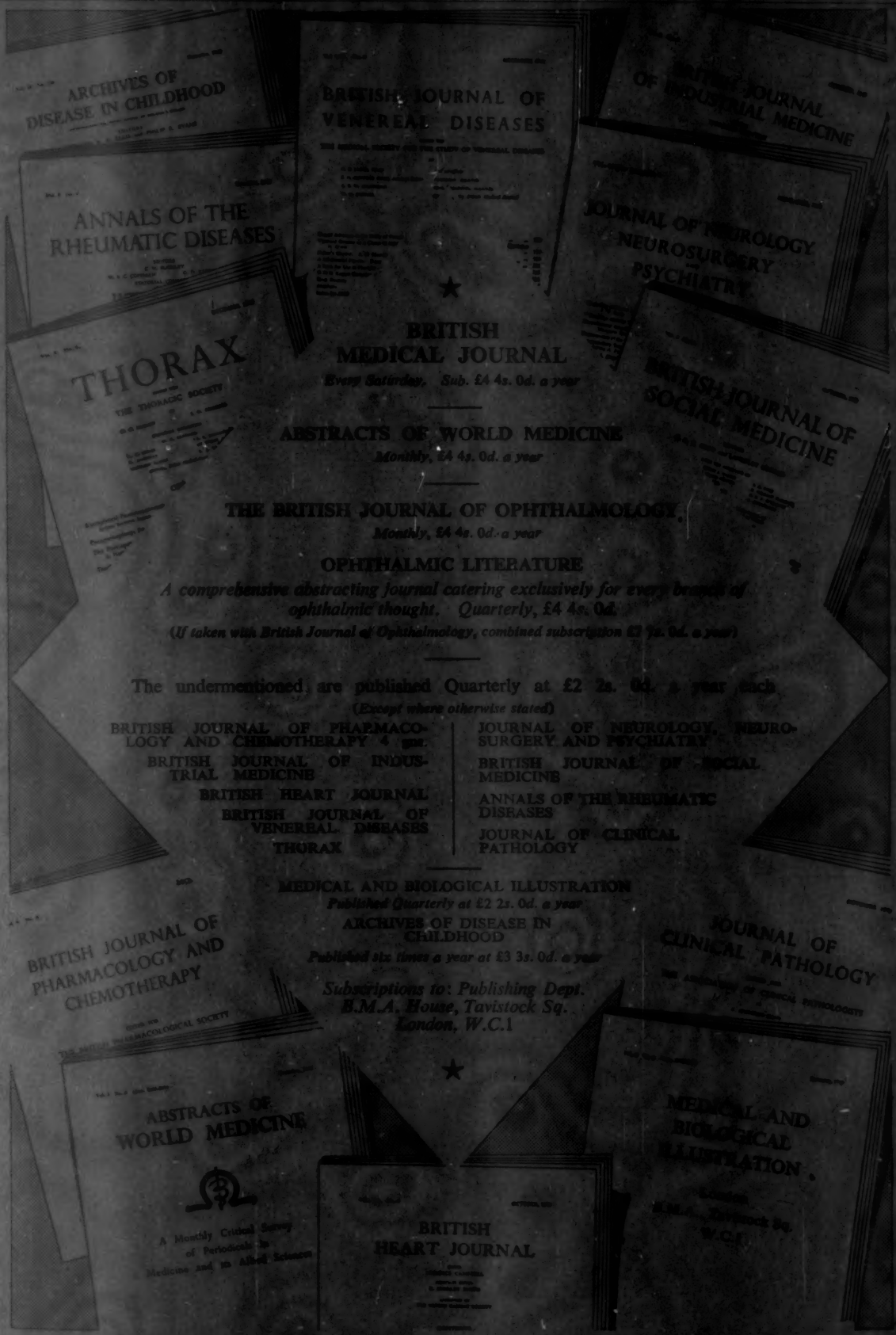
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